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JANUARY–JUNE 1974

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Printed in the United States of America

American Heart Journal

January 1974

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AMA Drug Evaluations 1971 First Edition
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PRECAUTIONS Potassium chloride should be administered with caution and adjusted to the requirements of the indi vidual patient since the amount of defi ciency and corresponding daily dose is often not known Excessive or even thera *peutic dosages may result in potassium* intoxication Patients should be frequently checked and periodic ECG and/or pla.ma potassium levels made High plasma con centrations of potassium ion may cause cardiac depression arrhythmias or arrest Use with caution in patients with cardiac disease In hypokalemic states attention should be directed toward the correction of the frequently associated hypochloremic alkalosis
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HOW SUPPLIED One pint and one gallon bottles

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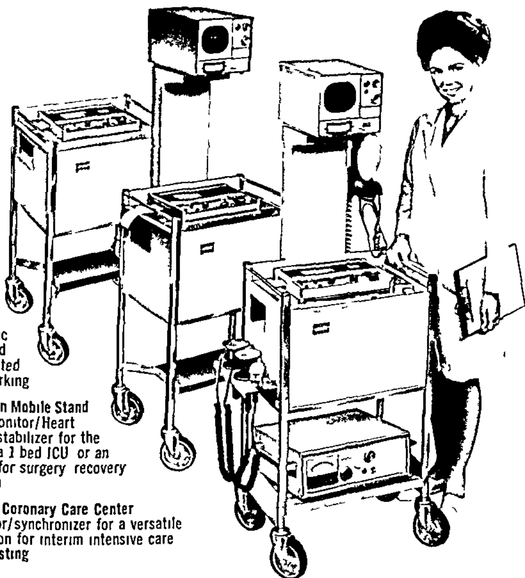
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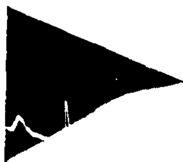
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American Heart Journal

March 1974

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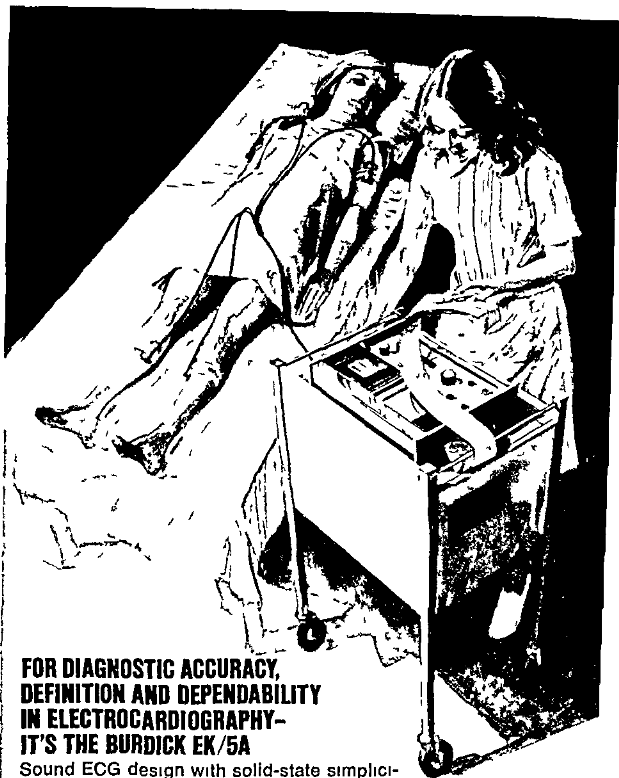
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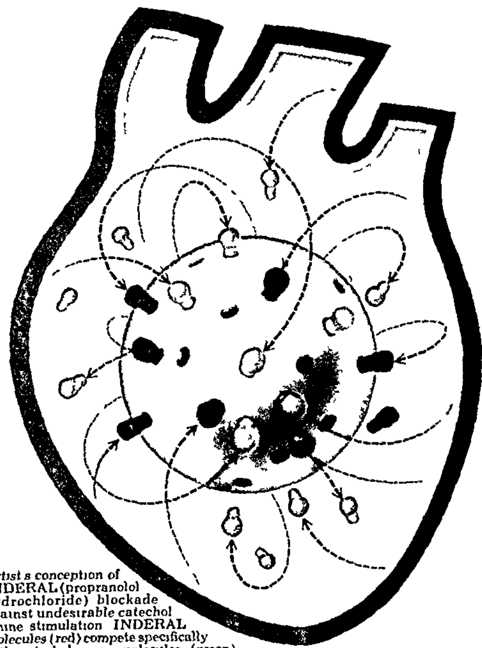


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When the heart is under catecholamine siege

INDERAL® Brand of propranolol hydrochloride

The beta-adrenergic blocking agent for many cardiac arrhythmias



Artist's conception of INDERAL (propranolol hydrochloride) blockade against undesirable catecholamine stimulation. INDERAL molecules (red) compete specifically with catecholamine molecules (green) for available beta receptor sites in cardiac tissue. With fewer catecholamine molecules gaining access to these sites, beta adrenergic stimulation is reduced *proportionately*.

As the first beta adrenergic blocking agent in clinical cardiologic use, INDERAL (propranolol hydrochloride) helps prevent or control catecholamine-induced supraventricular cardiac arrhythmias by means of a unique mechanism of action.

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With its unique site of action INDERAL does not interfere with the *therapeutic actions of nonadrenergic* cardiotonic agents. Thus INDERAL *can be used in combination—or alone—* to control arrhythmias when other *drugs have failed to produce a satis*factory response.

INDERAL is *especially effective in* the management of catecholamine-*induced supraventricular arrhythmias*. The response of ventricular arrhythmias *is generally less predictable*. INDERAL has proved to be of particular *value in the control of* digitalis-induced arrhythmias.

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April, 1974

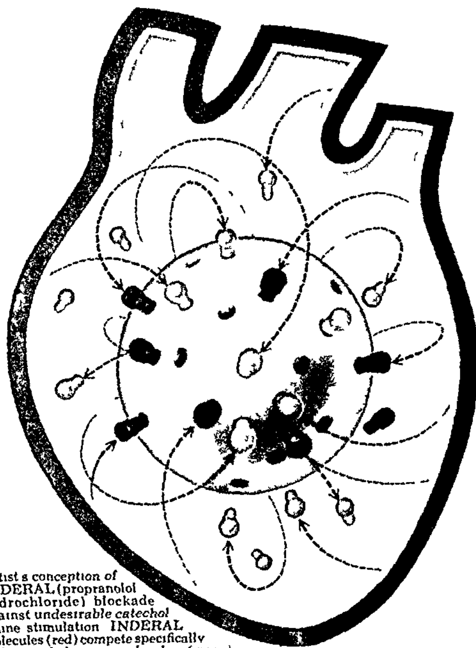
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The patient with cardiac arrhythmia may need medication most when he's least likely to take it...

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Quinaglute[*] *Dura-Tabs*[*] *(quinidine gluconate)*
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Precautions The precautions to be observed include all those applicable to quinidine A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine Hypersensitivity to quinidine although rare should constantly be considered especially during the first weeks of therapy

Signs of idiosyncrasy include febrile reactions skin eruptions thrombocytopenic purpura and respiratory embarrassment Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure with digitalis intoxication or renal insufficiency It should be administered cautiously if at all to senile patients Hospitalization for close clinical observations electrocardiographic monitoring and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours higher blood levels than necessary for maintenance of normal sinus rhythm could be reached whereas with 1 tablet every 12 hours the blood levels may be too low to maintain normal sinus rhythm

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Dosage For the prevention of premature atrial nodal or ventricular contractions the dose usually ranges from 1 to 2 tablets every 8 or 12 hours

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(quinidine gluconate) 5 gr (0.33 Gm)

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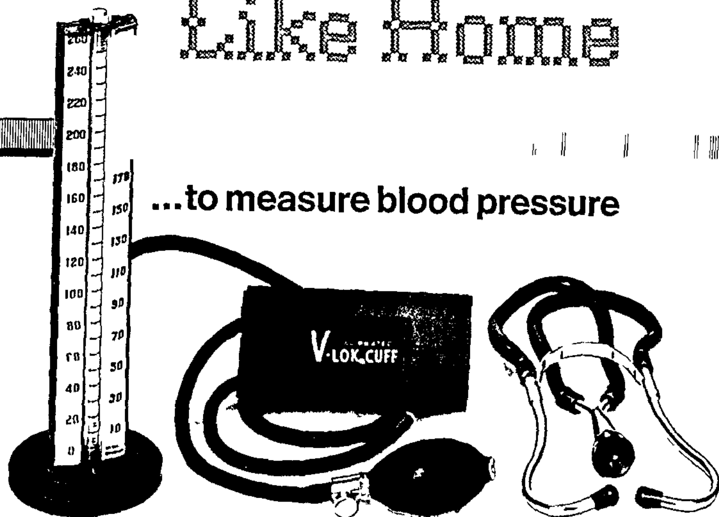
American Heart Journal

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There's No Place Like Home



HI/LO™ Baumanometer® Blood Pressure Kit

An increasing number of physicians in private practice and hypertension clinics are recommending that hypertensive patients have their blood pressure measured at home to supplement measurements made in the doctor s office or clinic Home recordings can help reveal the true level of a patient s blood pressure and assist the physician in regulating dosage of antihypertensive drugs [1]

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(1)Reference *Medical World News* *Cardiovascular Review 73* Burch G E Chairman Department Medicine Tulane University School of Medicine New Orleans Louisiana

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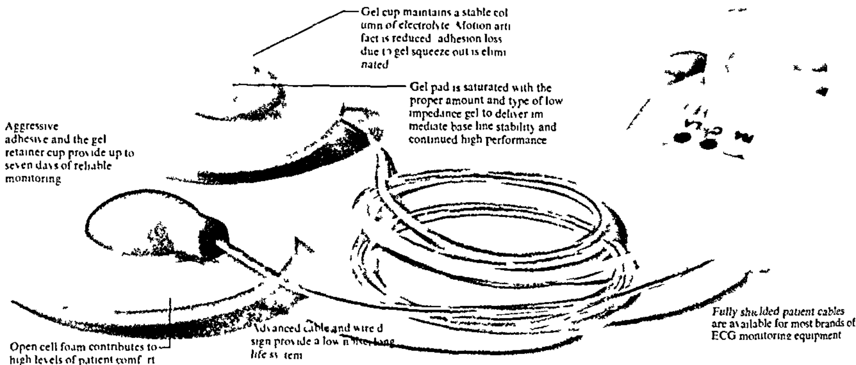


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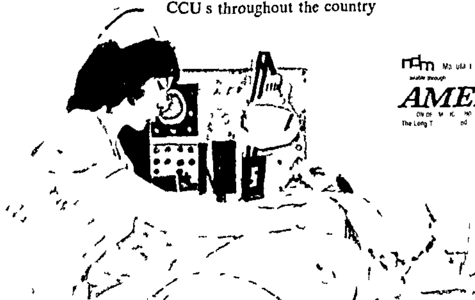
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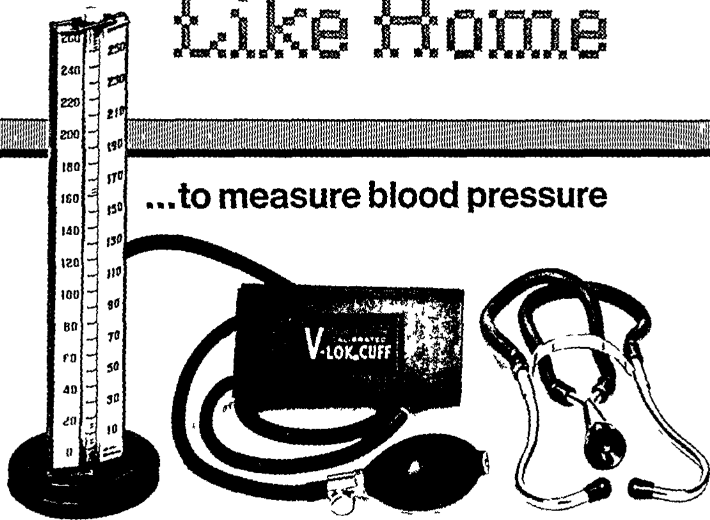
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AMERICAN HOSPITAL SUPPLY



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American Heart Journal

January 1974 Volume 87 Number 1

Editorial

The value of clofibrate in coronary heart disease

P M S Gillam MD MRCP*

Salisbury England

There is now good evidence that hyperlipidemia is associated with an increased susceptibility to coronary heart disease[1,2] There is evidence too that diets high in saturated fat are associated with both hyperlipidemia and coronary heart disease[3,4] Attempts to prevent coronary heart disease by dieting have met with uncertain and at the best only modest success[5] The search therefore continues for a safe and effective drug which will reduce serum lipid levels in the hope that it will thereby improve the prognosis in coronary heart disease Clofibrate is one of the latest of these drugs

There is no doubt that clofibrate reduces serum lipid levels[6,7] It is also claimed to have a beneficial effect on plasma free fatty acids plasma fibrinogen fibrinolysis and platelet stickiness[8] though there is considerable doubt about some of these functions[9] Its mode of action remains uncertain It seems a sensible hypothesis that treating patients who have angina or have suffered a myocardial infarct with clofibrate will improve their prognosis and slow the progression of their disease Three trials to test this hypothesis have recently been published The purpose of the first, from Newcastle[10] was to find out whether the drug clofibrate which has been shown to return raised lipoprotein levels towards normal had any effect on the morbidity and mortality of patients with established ischaemic heart disease [10] The purpose of the second, from Scotland,[11] was to test the value of reducing serum lipids in patients with ischaemic heart disease [11] and of the third, from the U.S.A [12] to determine the effect of the lipid lowering agent, clofibrate on the morbidity and mortality in primary atherosclerotic heart disease [12]

The general principles of the design of trials to test methods of medical treatment should now be considered The ever increasing complexity and expense of medical treatment is leading to the belief that medical methods must inevitably be more strictly monitored and managed.[13,14] Monitoring of hospital practice is already far advanced in the U S A and is advancing in Great Britain Stricter control is likely to follow It is therefore vital that our methods should be as soundly based as possible

The scientific method, if strictly applied, means stating and testing an hypothesis—thus that drug *A* will prolong the lives of patients with such and such a disease or that drug *A* will cause such and such a biochemical change Unless drug *A* is effective in the very great majority of cases (when it may be adequate to compare treatment now with no treatment in years gone by) it is essential to compare patients allotted *at random* to treatment and placebo The

From the Salisbury General Hospital, Salisbury Wiltshire England

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*Consultant Physician, Salisbury General Hospital, Salisbury England.

WHEN YOUR DIGITALIZED PATIENT NEEDS A DIURETIC



demonstrate that lowering serum cholesterol levels with clofibrate alters the prognosis in patients who suffer from angina or who have had a myocardial infarction No conclusions can be drawn from the Scottish trial about the efficacy of clofibrate because of an unfortunate mismatch of the treated and untreated groups The Newcastle trial appears to show a reduction in sudden deaths in patients who have suffered angina Neither trial showed an over all reduction in non fatal infarcts the combination of results from both trials to produce a significant figure[19] cannot be justified because of the differences of design and conduct The mode of action of clofibrate is unknown

It should be pointed out that the number of patients in whom this effect has been demonstrated is small 192 in the placebo group and 183 in the treated group It has been calculated[20] that a total of 2 000 patients would have to be studied to answer the question whether clofibrate helps patients with angina

The American trial[1] compared 518 men treated with clofibrate with 550 men left untreated A reduction in non fatal myocardial infarction rate from 6 6 per 1 000 per year to 1 89 per 1 000 per year is claimed There was no significant difference in mortality rate Patients and controls were pair matched for various risk factors but were not randomly allocated to the two groups Strictly therefore no credence can be given to the results of the trial Other criticisms can be made there is no evidence that the untreated patients were given placebo no information is given about change in weight or smoking habits in the treated and untreated groups the diagnosis of myocardial infarction was made by the patient s physician who may have known whether or not the patient was taking clofibrate There are more points which could be criticized Truthfully and sadly this immense trial never achieves the status where such criticism is of any consequence because it fails on the first and vital point of randomization Furthermore these authors describe a study of two other very large groups of over 1 000 men one of which is being treated and the other not They present comparisons and draw conclusions which are scientifically unjustified. It is hard to believe that this work will ever produce valid evidence about the efficacy of clofibrate

The place of clofibrate in the primary prevention of coronary heart disease remains to be established

Summary

What can the physician conclude from all this confusion and what should his practice be? First there is no absolute indication for the use of clofibrate in patients with coronary heart disease Second there is no evidence that lowering lipids by the use of clofibrate helps such patients therefore hyperlipidemia in these patients is not an indication for treatment. Third there is no evidence that clofibrate helps patients who have had a myocardial infarction but do not have angina whatever their serum lipid level Fourth one trial suggests that clofibrate may prevent sudden death in patients who have angina by some mechanism other than its effect on lipids Fifth there is no study of the use of clofibrate in patients over the age of 65 years Therefore the use of clofibrate should be confined to patients with angina under the age of 65 No great claims for this drug can be made since its efficacy may be slight once clinical coronary heart disease is established and any beneficial result remains to be confirmed. However clofibrate is a safe drug and many will feel that patients should be given the benefit of any doubt They will therefore use the drug until there is definite evidence that it does no good.

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11 Ischaemic Heart Disease a secondary prevention trial

groups of patients must be identical, the investigator should demonstrate their identity after random allocation, and they must be treated identically in all other ways This last proviso means that if possible a double blind technique should be used All this is particularly important when studying a multifactorial disease such as coronary heart disease, particularly important when studying a disease where emotion may play a part, and particularly important when the judgment of end points may be affected by unconscious observer bias (for instance, "probable re infarction") Only then may statistical tests of significance be applied [15]

All this may seem to readers to be but glimpses of the obvious Suffice it to say that by 1969 only two of the innumerable studies of anti coagulants obeyed the basic rule of random allocation [16] that trials that fail in this simple respect are still regularly reported in the most respectable journals (e g *Lancet*[17]) and that the largest of the trials here to be considered is also ruined by failure to obey this rule

Furthermore having tested an hypothesis and found it incorrect or of little clinical value workers are often tempted to subject their data to reanalysis they rearrange groups subtract and add patients to them, add different end points into a horrible conglomerate called 'all events,' and with the aid of a computer search for associations hitherto undreamt of Both the British trials[10, 11] fall into this error It has been pointed out that this procedure will inevitably throw up some chance associations [18] (Indeed, the finding that clofibrate worsened the prognosis in men who had had an infarct was considered by the Scottish authors[11] to be 'presumably a chance finding')

The two British trials[10, 11] were published side by side in the same number of the *British Medical Journal* There were 15 main differences in design and 5 main differences in conduct of the two trials The report from Newcastle[10] claimed a significant over all reduction in sudden deaths (death immediate or within a few minutes) and all deaths and in non fatal infarcts in the clofibrate treated group This was a well designed randomized double blind trial spoiled by very complex combination and permutation of patients and results Analysis shows that the difference in mortality rates is due to a reduction in sudden death but this is only significant if patients on anticoagulants are included and in patients who have a history of angina and an infarct conversely the difference in nonfatal infarctions is only significant if patients on anticoagulants are excluded, and then only in the group with angina who have *not* had an infarct There was no protection against death or infarction in patients who had had a previous infarction but no angina

A number of other criticisms of this trial have been made, patients with a diagnosis of angina by history alone were included many more patients in the clofibrate group withdrew from the trial and the fate of those who withdrew is not recorded, and only cardiac deaths are recorded. This trial showed no relationship between protection and the lipid lowering effects of clofibrate

The Scottish report[11] claims a significant reduction in sudden death (death within one hour) and all deaths in those patients treated with clofibrate who were admitted to the trial with a history of angina alone or with angina plus myocardial infarction

Results are presented of two sub trials a 'double blind' comparison of patients randomly allocated to treatment and placebo groups and a trial of patients also treated with anticoagulants who were not assessed on a double blind basis but who were randomly allocated. The results from these two sub trials were also combined, but this cannot be justified because of the different conduct of the two sub trials Unfortunately the random allocation in the 'double-blind' sub trial failed to produce two identical groups in two important respects serum cholesterol and diastolic blood pressure were significantly higher in the placebo group This means that strictly no conclusion as to the efficacy of clofibrate can be drawn from this sub trial In the 'anticoagulant' sub trial there was no significant reduction in mortality rate or in non fatal infarcts among the patients treated with clofibrate

Furthermore there was no relationship between the chance of sudden death and whether or not cholesterol was lowered by clofibrate Therefore this trial may be said to show that lowering serum cholesterol with clofibrate has no effect on the prognosis in coronary heart disease

To summarize both these trials have failed to

demonstrate that lowering serum cholesterol levels with clofibrate alters the prognosis in patients who suffer from angina or who have had a myocardial infarction. No conclusions can be drawn from the Scottish trial about the efficacy of clofibrate because of an unfortunate mismatch of the treated and untreated groups. The Newcastle trial appears to show a reduction in sudden deaths in patients who have suffered angina. Neither trial showed an over all reduction in non fatal infarcts; the combination of results from both trials to produce a significant figure[19] cannot be justified because of the differences of design and conduct. The mode of action of clofibrate is unknown.

It should be pointed out that the number of patients in whom this effect has been demonstrated is small: 192 in the placebo group and 183 in the treated group. It has been calculated[20] that a total of 2 000 patients would have to be studied to answer the question whether clofibrate helps patients with angina.

The American trial[12] compared 518 men treated with clofibrate with 550 men left untreated. A reduction in non fatal myocardial infarction rate from 6 6 per 1 000 per year to 1 89 per 1 000 per year is claimed. There was no significant difference in mortality rate. Patients and controls were pair matched for various risk factors but were not randomly allocated to the two groups. Strictly therefore, no credence can be given to the results of the trial. Other criticisms can be made: there is no evidence that the untreated patients were given placebo; no information is given about change in weight or smoking habits in the treated and untreated groups; the diagnosis of myocardial infarction was made by the patient's physician who may have known whether or not the patient was taking clofibrate. There are more points which could be criticized. Truthfully and sadly this immense trial never achieves the status where such criticism is of any consequence because it fails on the first and vital point of randomization. Furthermore these authors describe a study of two other very large groups of over 1 000 men, one of which is being treated and the other not. They present comparisons and draw conclusions which are scientifically unjustified. It is hard to believe that this work will ever produce valid evidence about the efficacy of clofibrate.

The place of clofibrate in the primary prevention of coronary heart disease remains to be established.

Summary

What can the physician conclude from all this confusion and what should his practice be? First, there is no absolute indication for the use of clofibrate in patients with coronary heart disease. Second, there is no evidence that lowering lipids by the use of clofibrate helps such patients; therefore hyperlipidemia in these patients is not an indication for treatment. Third, there is no evidence that clofibrate helps patients who have had a myocardial infarction but do not have angina, whatever their serum lipid level. Fourth, one trial suggests that clofibrate may prevent sudden death in patients who have angina by some mechanism other than its effect on lipids. Fifth, there is no study of the use of clofibrate in patients over the age of 65 years. Therefore the use of clofibrate should be confined to patients with angina under the age of 65. No great claims for this drug can be made since its efficacy may be slight once clinical coronary heart disease is established and any beneficial result remains to be confirmed. However, clofibrate is a safe drug and many will feel that patients should be given the benefit of any doubt. They will therefore use the drug until there is definite evidence that it does no good.

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Clinical communications

Systolic and diastolic time intervals in pulsus alternans

Significance of alternating isovolumic relaxation

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The term pulsus alternans (PA) implies one to one alternation of strong and weak ventricular systoles originating from a fixed pacemaker and not influenced by respiration[1] PA appears in patients with borderline ventricular reserve or frank heart failure especially in conditions like aortic stenosis hypertension coronary artery disease and the cardiomyopathies[1 5] Very rarely it occurs without evidence of heart disease PA has been induced experimentally in dogs[6 10] and studied in humans during cardiac catheterization[11 14] and rarely utilizing external polygraphic techniques[1 15] Clinically it is detected by palpation of alternating strong and weak pulses at the easily accessible arteries (radial brachial femoral carotid)

The PA phenomenon offers a unique opportunity to study cardiac dynamics in a diseased heart without manipulating its environment—i e with the patient acting as his own beat to beat control Investigations utilizing external polygraphic techniques are particularly suited to beat to beat analysis of physiologically significant parameters of cardiac function We studied 14 patients with PA associated with various kinds of heart disease (Table I) using external polygraphic tracings

The present study amplifies limited early observations on alternation of left ventricular systolic intervals[1] extends them to include the first derivative of the carotid displacement pulse[16] and reports new observations on alternation of diastolic intervals In a previous report[1] two out of four patients with PA showed marked alternation of the isovolumic relaxation period (IRP) In this new study 7 out of 8 patients had alternating IRP Moreover this is shown to occur at the expense of the rest of diastole demonstrating for the first time independent alternation of intervals within fixed durations of diastolic as well as systolic periods

Methods definitions abbreviations (Fig 1)

The electrocardiogram (ECG) phonocardiogram (PCG) apexcardiogram (ACG) and carotid pulse curves were recorded and the following measurements were made in each of six to ten consecutive cardiac cycles—i e three to five each of strong beats (SB) and weak beats (WB) were measured and averaged Apexcardiograms and phonocardiograms were recorded via a Sanborn No 21050 A/B signal splitting pulse microphone (time constant over 3 seconds)

Cycle length The R R interval of the ECG expressed in milliseconds

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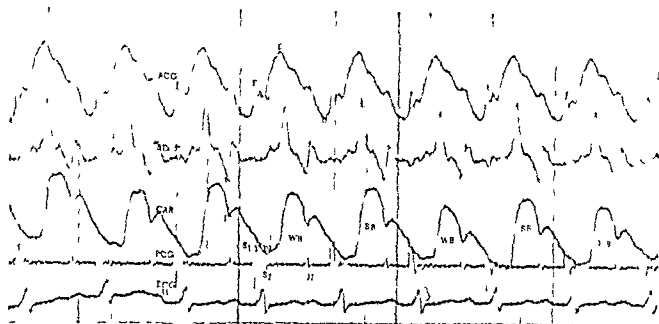


Fig 1 External polygraphic tracing of a patient with pulsus alternans *ACG* = apexcardiogram *u* = upstroke *F* = filling wave *A* = atrial wave *E* = maximum systolic peak *O* = *O* point *dD dt* = first derivative of carotid displacement pulse *P* = peak amplitude *N* = nadir *T* = total amplitude (i e P+N) *CAR* = carotid pulse tracing *u* = upstroke *In* = incisura *PCG* = phonocardiogram *ECG* = electrocardiogram (Lead II) Note the alternation of *ACG (A E,F)* *dD/dt (P N T)* and *CAR* amplitude Also note *F* of *ACG* which coincides with S_{III} of *PCG* thus confirming that it is the filling wave

Table I *Clinical diagnosis of patients with pulsus alternans*

Case no	*Diagnosis*
1	Hypertensive heart disease
2	Arteriosclerotic heart disease
3	Hodgkin s disease
4	Alcoholic cardiomyopathy
5	Cardiomyopathy (? etiology)
6	Chronic obstructive lung disease
7	Alcoholic cardiomyopathy
8	Anemia
9	Rheumatic heart disease
10	Coronary artery disease
11	Arteriosclerotic heart disease
12	Coronary artery disease
13	Arteriosclerotic heart disease
14	Coronary artery disease

q Initiation of the QRS complex in Lead II whether a q wave or the beginning of the R upstroke In practice because of occasional baseline artifacts a large number of complexes were inspected and the q to R peak (or R upstroke to R peak) time was ascertained so that curves could be timed from the precisely registered R peak the q to R peak was then added in the calculations q was thus the zero point for all measurements in each cycle

ACGu Timing of the apexcardiogram (ACG) upstroke

I_M Timing of the first high frequency (mitral) oscillation of the first heart sound

CARu Timing of the onset of the rapid portion of the carotid (CAR) upstroke

II_A Timing of the first high frequency (aortic) component of the second heart sound

CAR_{In} Timing of the carotid incisura

O Timing of the O point of the apexcardiogram

Calculations As described previously[1] the following parameters were calculated from the foregoing measurements electromechanical systole (EMS) pulse transmission time (PTT) pre ejection period (PEP) including isovolumic contraction time (IVCT) and Q Im interval left ventricular ejection time (LVET) ejection time index (ETI), isovolumic relaxation period (IRP) diastolic filling period (DFP) and pre ejection period divided by left ventricular ejection time (PEP/LVET) Total diastole (TD) was taken as IRP + DFP preceding a given beat

In addition the first derivative of the carotid displacement pulse (dD/dt) was recorded in 11 patients using apparatus and methods described

Table II Summary of results

	No	*SB* Mean ± SD	*WB* Mean ± SD	PΔ
BP systolic	8	135 9 ± 43	119 1 ± 38 9	< 001
diastolic	8	81 1 ± 33 5	80 3 ± 33 6	NS
HR	14	104 86 ± 26	106 9 ± 23 7	NS
PEP	14	129 4 ± 20 5	145 6 ± 22 3	001
Q I_M	14	75 4 ± 17 2	76 4 ± 17 2	NS
IVCT	14	56 4 ± 19 1	70 2 ± 24 7	< 001
EMS	14	329 5 ± 59 4	327 2 ± 57 6	NS
LVET	14	211 4 ± 32 9	192 9 ± 31 4	< 001
ETI	14	342 4 ± 23 7	327 4 ± 26 5	< 001
PEP/LVET	14	0 619 ± 0 089	0 757 ± 0 130	< 001
TD	8	303 ± 104 8	291 8 ± 91 7	NS
DFP	8	214 5 ± 100 6	195 88 ± 88.5	< 02
IRP	8	95 9 ± 29	88 5 ± 29	< 02
dD/dt T amp	11	31 27 ± 12 2	25 89 ± 11 1	< 001
dD/dt P amp	11	20 07 ± 7 4	15 25 ± 6 5	< 001
%P/T	11	0 664 ± 0 107	0 5818 ± 0 066	< 005
%dD/dt (=P/T × 100)		66 5 ± 10 7	58.2 ± 6 6	< 005

Abbreviations SB = strong beat, WB = weak beat, BP = blood pr ssure HR = heart rate PEP = pre-ejection period, IVCT = isovolumic contract on time EMS = electromechanical systole LVET = left v ntricular ejection time ETI = eject on time index TD = total d astole DFP = diastolic filling period, IRP = isovolumic relaxation period, dD/dt T amp = total amplitude of derivati e dD/dt P amp = ampl tude of peak of carotid derivative NS = not statistically significant

elsewhere[16] No apexcardiogram was recorded in 6 patients because of difficulties in obtaining a technically satisfactory curve

Results

These are summarized in Table II which shows mean figures for strong beats (SB) and weak beats (WB) differences and standard deviations (S D)

Blood pressure There was a slight to moderate increase in the systolic blood pressure in the SB compared to the WB the changes in the diastolic pressures were small (SB = systolic 135 9 WB = systolic 119 1 P < 0 001 diastolic SB = 81 3 WB = 80 2 P < 0 2) It was technically difficult to ascertain different diastolic levels in most cases

Cycle length (R R) and heart rate (HR) either showed biologically insignificant changes or the rates were identical in the SB s and WB s (The P value of < 05 occurred because minuscule differences in 7 patients were in the same direction)

Total diastole (TD) was not significantly different between the SB and WB (SB = 303 WB = 291 8 P < 0 2)

Diastolic filling period (DFP) was significantly longer in the beats preceding the SB (SB = 214 5 WB = 195 9 P < 0 02)

Isovolumic relaxation period (IRP) was significantly prolonged in the SB compared to WB (SB = 95 9 WB = 88 5 P < 0 02)

Pre ejection period (PEP) was abnormally prolonged in all cases but was more prolonged in the WB than in SB (SB = 129 4 WB = 145 6 P < 0 001)

Pep components

Q Im although usually abnormally long showed no significant changes between SB and WB (SB = 75 4 WB = 76 4 P < 0 5)

IVCT alternation was the basis of PEP alternation It was uniformly prolonged in the abnormal range in the SB as well as the WB but more so in the WB (SB = 56 4 WB = 70 2 P < 0 001)

Left ventricular ejection time (LVET) fell in the WB In both the SB and the WB the LVET was abnormally short for heart rate (SB = 211 4 WB = 192 9 P < 0 001)

Electromechanical systole (EMS) showed no significant change (SB = 329 5 WB = 327 2 P < 0 5)

Ejection time index (ETI) alternated in parallel

with LVET as expected from the identity of cycle length in both SB and the WB ETI was below pre dicted normal in both the SB and the WB (SB = 342 4, WB = 327 4, P < 0 001)

PEP/LVET was abnormally large the abnor mality being more pronounced in the weak beats (SB = 0 6193 WB = 0 7571, P < 0 001)

Amplitude of peak of carotid derivative (P) was consistently higher in the SB than in the WB (SB = 20, WB = 15 2 P < 0 001)

Total amplitude of derivative (T) showed changes in the same direction as P

P/T this ratio expressed as per cent of peak to total amplitude of the derivative (% dD/dt) was reduced in the WB compared to SB (SB = 0 6645 WB = 0 5818, P < 0 001)

Discussion

Limitations of indirect methods Noninvasive methods have the advantages of obtaining car diac functional indices safely and painlessly and may be repeated as often as necessary They have the disadvantage that the results reflect certain hemodynamic parameters but are not in themselves proved sources of basic data (except ing the time based measurements)

Pulsus Alternans (PA) appears to involve one or both of two major mechanisms (1) Frank Starling principle within limits pre load—i e increased stretch (greater initial length) of mus cle fiber results in stronger contraction and (2) the myocardial theory alternating changes in the beat to beat contractile state of muscle fibers either involving the entire myocardium or due to alternating deletion of fractional contrac tions Our results were consistent with both mechanisms

Alternating systolic time intervals Abnormal PEP as seen in both SB s and WB s was due to prolonged IVCT, compatible with the decreased rate of contractile element shortening in a diseased ventricle Further IVCT prolongation in the WB s would indicate further reduction of cardiac performance during this event unless preload changes (which cannot be determined indirectly) The virtually unchanged Q Im in both the SB s and the WB s indicated that the ventricle overcomes atrial pressure (accounting for mitral valve closure) within the same time periods in the SB's and WB s On the other hand greater prolongation of IVCT in the WB s than in the SB s indicates that weaker ventricular contractions take longer to make cavitary pres sure reach and surpass aortic pressure to com mence ventricular ejection Such changes can be due either to depressed inotropic state to reduced end diastolic stretch or both

Insignificant fluctuations in cycle length elimi nated rate related changes in the LVET Car diac catheterization studies[17] including aortic flow studies[18] have shown that LVET has a close correlation with stroke volume (SV) Although LVET was decreased for the corresponding HR (ETI = 376 ± 1 2 HR)[1] in all beats the SB showed a longer ETI (corresponding to a larger SV) compared to the WB

Relationship among EMS LVET PEP Within a stable or insignificantly changed EMS (in all but Case 7) PEP and LVET varied reciprocally The longer PEP and shorter LVET in weak beats in the presence of a fixed EMS is consistent with depressed ventricular function[25,26] Expressed as a ratio—i e PEP/LVET, this relationship has been shown to reflect most closely the ejection fraction[26] Therefore the higher the ratio the smaller the ejection fraction and the more the depression of ventricular performance The SB and the WB showed the appropriate di rectional changes for this ratio Alternating IVCT shorter in the SB than in the WB implies that the rate of ventricular contraction (contrac tile element shortening rate) is faster in the SB than in the WB This has been established in hemodynamic studies in dogs[12,14] and in humans[9,13] by observation that the rate of circumferential fiber shortening (or Vcf) was faster in the SB than in the WB At any level of inotropy this may be the result of changes in preload (i e , Frank Starling mechanism) Conversely with a fixed preload this can reflect alternating contractile state

Relationship of dD/dt to PEP Observations on the first derivative of the carotid displacement pulse[16] can be explained on the basis of both changing contractile state and changing preload in PA The rate of rise of the carotid displace ment pulse expressed as the relative (%) size of its first time derivative (dD/dt) has been shown to reflect changes in left ventricular perfor mance which are also reflected in changes in PEP (mostly IVCT)[16] The normal range estab lished from this laboratory was 75 ± 8 9 per cent (S D) and the range in a series of patients with various heart diseases was 64 4 per cent ± 4 26 per cent (both figures are expressed as per cent

IRP P₅ < 02	DFP P₅ < 02	TOTAL DIASTOLE (IRP + DFP) P₅ N S
88 5	214 5	303 0
95 9	195 9	291 8

Mean DFP preceding and IRP of weak beat (WB) [hatched]

Mean DFP preceding and IRP of strong beat (SB) [open]

Fig 2. Relationship of components of total diastole Total diastole is composed of *IRP + DFP (DFP belonging to the next beat—i e its filling time)* Total diastole for strong (SB) and weak (WB) beats is statistically equal though *DFP* is shorter preceding the weak beat owing to encroachment by *IRP* of the strong beat.

of peak (P) to total (T) amplitude of the derivative—i e P/T × 100) Mean values of dD/dt for this study are SB = 66 45% WB = 58 18% Although some of the values fall in the low normal range the consistent finding is of a higher peak amplitude and per cent dD/dt in the SB compared to WB The previous study showed that isoproterenol in inotropic agent increased per cent dD/dt while propranolol an anti inotropic agent had the opposite effect Similarly inotropic agents abolish PA[9,27] and anti inotropic agents promote it.[7] The changes in per cent dD/dt are therefore consistent with (but not proof of) alternating inotropic state in PA

Alternating diastolic intervals The DFP preceding the SB was *consistently longer* than the one preceding the WB (mean SB = 214 5 msec WB = 195 9 msec P < 02) In the absence of extreme reduction in compliance longer DFP should produce a larger end diastolic volume (EDV) preceding the SB However although quantitative DFP alternation was statistically significant the mean change (18 6 msec) might not have been biologically significant since most filling occurs early Thus any shortening if it occurred in the flat (late) part of the filling curve would have little effect (as in tachycardia) and it is not possible to demonstrate by indirect methods which filling phase was actually abbreviated

Alternation of filling could explain at least in part the increased LVET (and presumably SV) of the SB in accordance with the Frank Starling principle particularly since strong beats have a faster ejection rate[19,20] (which by itself would tend to reduce LVET) Catheterization data in humans and experimental animals give conflicting results with regard to EDV since some workers have shown a changing EDV in PA[12,21,22] while others have observed no such changes[14,23] Our results can be interpreted as compatible with the former and hence favor explanation of PA at least partly on the basis of the Frank Starling principle Since actual DFP s are but rarely measured we cannot know the effects of prolonged filling in the hemodynamic studies of PA cited Filling effects are especially complex because reduced compliance may restrict actual filling to an especially brief period which in extreme cases might make the volume of filling independent of its duration In this connection the relationship between DFP and IRP is pertinent

Relationship between DFP and IRP (Fig 2) Total diastole (TD) is represented by IRP plus DFP While IRP is a function of the beat in which it is measured and the DFP affects the next beat they appear to have a unique reciprocal relationship in pulsus alternans Thus for example the total diastole before the SB equals its own (preceding) DFP plus the IRP of the preceding WB (i e TD = II_A—ACGu) Actual measurements DFP SB = 214 5 WB = 195 9 IRP SB = 95 9 WB 88 5) Total diastoles preceding both the SB and the WB were not significantly different (P = 0 2) although the DFP s and the IRP s were different (P < 0 02 in each case) It is obvious then that the sum of the IRP of the WB plus the DFP of the succeeding SB was approximately equal to the sum of the IRP of the SB plus the DFP of the succeeding WB (Fig 2) Since the

duration of systole was fixed, the shorter DFP preceding the weak beat could only be due to encroachment by the IRP of the strong beat Therefore, the major time change within total *diastole that might account for any alternation* in EDV is attributed to alternating IRP Thus it is not the longer ejection period that encroaches upon the following DFP as has been erroneously proposed[8], it is the IRP that does this DFP in some cardiac catheterization studies has been measured from the aortic incisura (equivalent to II_A) which is inaccurate, since this actually includes the IRP and is therefore a measure of total diastole (TD) External polygraphic techniques afford a more accurate measure of DFP—i e, from the O point of the ACG to the next upstroke, while IRP is measured from II_A to O in *the same cycle* (Fig 1)

Summary

Systolic and diastolic time intervals in 14 cardiac patients with pulsus alternans revealed significant alternation of PEP IVCT LVET ETI PEP/LVET and carotid dD/dt, with better functional values in the strong beats Cycle length duration of electromechanical systole (EMS) and total diastole (TD) did not alternate A new observation alternation of the components of total diastole—i e isovolumic relaxation period (IRP) and diastolic filling period (DFP) occurred *in 7 out of 8 patients These diastolic intervals* alternated reciprocally such that the IRP of the strong beats encroached upon the DFP of the next (weak) beats

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Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease

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The fourth heart sound (S_4) is traditionally considered an abnormal finding and by its very presence a presystolic gallop [1-4] Because bedside auscultation frequently appeared to reveal an S_4 in older patients who were free of signs and symptoms of heart disease we designed a prospective completely blinded phonocardiographic investigation

Material and methods

We investigated 250 consecutively examined ambulatory subjects of the Framingham Heart Study aged 50 to 82 years (mean age 64 0 years) Phonocardiograms (Schwarzer No P622) were recorded at a paper speed of 50 mm per second with nominal filter peaks of 35 70 and 140 Hz and respective slopes of 7 5 18 and 24 db per octave The microphone has a flat response from 20 to 1 000 Hz with a rolloff of only 3 db per octave Clinical data and diagnosis were those independently arrived at during a 20 year period of routine visits Heart disease was excluded by absence of appropriate history and of abnormalities on the following physical examination by two physicians ECG and chest x ray film No clinical data were revealed until all phonocardiograms (PCG s) were recorded and studied and all results were tabulated S_4 was defined as distinct low frequency vibrations consistently following every atrial systole and preceding the QRS of the ECG in patients with sinus rhythm (Figs 1 and 2) PCG s were scored S_4— yes or no and the diagnostic data were independently scored cardiovascular disease— yes or no The results were then matched.

Results

Five of the 250 subjects proved to have atrial fibrillation The results in the remainder all with sinus rhythm are summarized in Table I

Among 93 subjects without cardiovascular disease 68 (73 1 per cent) had an S_4 while among 153 with cardiovascular disease an S_4 was recorded in 113 (74 3 per cent) virtually an identical prevalence The Chi square (χ^2) test for presence or absence of S_4 *versus* presence or absence of cardiovascular abnormality demonstrated no significant difference in distribution

Discussion

Fourth heart sounds were no more common with or without heart disease in this group of 50 to 80 year old individuals Because of the strictly blind design of the study it is unlikely that bias could have entered into the recording or interpretation of the PCG s The presence of an S_4 as a potentially normal finding denies the traditional concept of S_4 as a reliable sign of cardiac abnormality in this age group Moreover the prevalence of S_4 of approximately 70 per cent irrespective of cardiac status is supported by certain other kinds of investigation Benchimol and Desser[5] reviewed the findings in 100 patients (age 17 to 67 years mean age 43 years) who underwent cardiac catheterization and coronary

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duration of systole was fixed the shorter DFP preceding the weak beat could only be due to encroachment by the IRP of the strong beat Therefore the major time change within total diastole that might account for any alternation in EDV is attributed to alternating IRP Thus it is not the longer ejection period that encroaches upon the following DFP as has been erroneously proposed[8] it is the IRP that does this DFP in some cardiac catheterization studies has been measured from the aortic incisura (equivalent to II_A) which is inaccurate, since this actually includes the IRP and is therefore a measure of total diastole (TD) External polygraphic techniques afford a more accurate measure of DFP—i e, from the O point of the ACG to the next upstroke, while IRP is measured from II_A to O in the same cycle (Fig 1)

Summary

Systolic and diastolic time intervals in 14 cardiac patients with pulsus alternans revealed significant alternation of PEP IVCT LVET ETI PEP/LVET and carotid dD/dt, with better functional values in the strong beats Cycle length duration of electromechanical systole (EMS) and total diastole (TD) did not alternate A new observation, alternation of the components of total diastole—i e isovolumic relaxation period (IRP) and diastolic filling period (DFP) occurred in 7 out of 8 patients These diastolic intervals alternated reciprocally such that the IRP of the strong beats encroached upon the DFP of the next (weak) beats

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Table I Prevalence of S_4 vs cardiovascular status—250 ambulatory subjects aged 50 to 80 years

	S_4 present	*S_4 absent*	*Totals*
No cardiovascular disease	68	25	93
Cardiovascular disease	113	39	152
	181	64	245
Coronary	65	24	
Hypertensive	46	15	
Hypertension alone	33	8	
Heart disease	13	7	
Rheumatic	2	0	
	113	39	
Atrial fibrillation			5

χ^2 test for distribution P NS

lar compliance Thus S_4 disappears if there is high grade A V valve stenosis or during atrial fibrillation (Atrial sounds can be heard and recorded following F waves in many cases of atrial flutter in which a coordinated atrial contraction does occur) An S_4 is the rule at all ages in ventricular hypertrophy perhaps the most common pathologic cause of decreased ventricular compliance The equal prevalence of S_4 among cardiovascular normals and abnormals after age 40 could be related to a physiologic aging change in myocardial compliance In this connection ventricular compliance has been defined as the magnitude of deformation of the ventricle resulting from an applied force[8] Advancing age might be associated with decreased ventricular distensibility[8] although there is no direct proof of this Provided there is no concomitant change in the dynamics of ventricular filling (the applied force) this could explain the normal S_4 in older persons

In children and young adults the third heart sound (S_3) associated with rapid filling in early diastole is quite normal and commonly present Its genesis as a normal phenomenon is not completely understood although like S_4 it requires reasonably free flow across the mitral and tricuspid valves S_3 however normally disappears during the third decade An abnormal S_3 (early diastolic gallop) appears in the presence of decreased ventricular compliance commonly with myocardial failure and most strikingly with restrictive or constrictive pericardial endocardial or myocardial lesions[9] An abnormal S_4 (presystolic gallop) in persons with ventricular abnormalities may be analogous in mode of production to an abnormal S_3

The problem of audibility This investigation was not concerned with auscultation An earlier study[10] involving mutually blinded auscultators and phonocardiographic interpreters disclosed that among 88 subjects with a recordable S_4 this was audible in 63 (72 per cent comparable with 80 per cent of recorded S_4 s in Benchimol and Desser s[5] series) Audibility was not related to frequency nor (surprisingly) to its relative amplitude (S_4 S_1 ratio) nor to the interval between S_4 and S_1 Audible fourth heart sounds were very significantly (P = 01) related to shorter P S_4 intervals the mean P S_4 was 112 9 msec for 63 audible *versus* 130 4 msec for 25 inaudible S_4 s

The audibility study served to raise more questions about current concepts of the S_4 than it answered For example the clinical implications of audibility per se remain unclear—i e in view of the lack of relationship of phonocardiographic amplitude to audibility when does an audible S_4 become a gallop? (We did not investigate palpability or ACG correlation) Moreover in view of the clear cut relationship between shorter P S_4 intervals and audibility what is the status of the earliest supposedly inaudible vibrations? Are these in fact audible or do they somehow contribute to the audibility of the subsequent vibrations? The audibility study made no prior assumptions and was the only blinded controlled study extant We believe that it has not completely settled any of these issues and

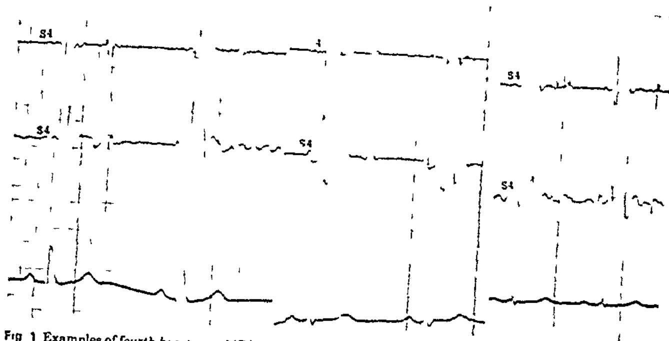


Fig 1 Examples of fourth heart sound (S_4) in patients with cardiac disease *Top to bottom* Phonocardiogram (70 Hz) phonocardiogram (35 Hz) electrocardiogram (Lead II) *Left panel* Coronary heart disease 76 year old woman *Middle panel* Coronary heart disease 62 year-old man *Right panel* Hypertensive heart disease 58 year-old man

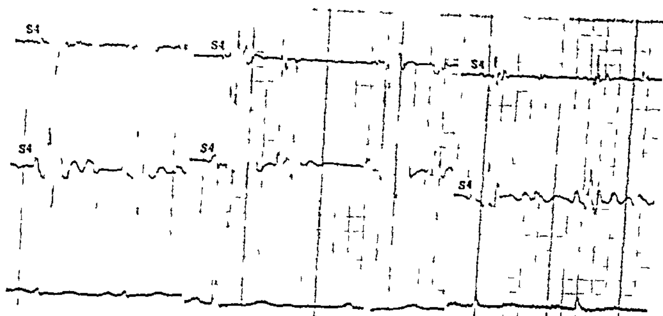


Fig 2 Examples of fourth heart sound (S_4) in three patients with no evidence of cardiovascular disease *Top to bottom* Phonocardiogram (70 Hz) phonocardiogram (35 Hz) electrocardiogram (Lead II)

cineangiography with normal results 75 (75 per cent) had an S_4 Caulfield and colleagues[6] found an S_4 in 88 (70 per cent) of 124 patients with aortic stenosis Both proportionate results are remarkably similar to those in both our groups Moreover in Caulfield's patients the S_4 was reliable evidence of severity of stenosis only under age 40, over age 40 S_4 was lost as a discriminator This is entirely consistent with the appearance of S_4 as an aging effect

The fourth heart sound like the third heart sound (S_3) is an event associated with ventricular filling Its occurrence is related to three known factors [7] (1) reasonably free forward flow across one or both A V valves (2) an effective atrial contraction and (3) diminished ventricu

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that they need to be settled Moreover it would be desirable to have confirmation or refutation by other controlled studies which equally seek to minimize observer bias since the results of auscultation for a frequently subtle phenomenon remain highly subjective Indeed to determine the actual audibility of particular vibrations it would be desirable to employ phono acoustic 'gating' to selectively blank out portions of S_4 and S_1 The present investigation addressed itself solely to the comparative phonocardiographic prevalence of S_4 among apparently normal and abnormal older individuals

Summary

A blinded prospective study of phonocardiograms revealed a fourth heart sound (S_4) in 181 of 245 consecutively examined ambulatory subjects in sinus rhythm aged 50 to 80 years whose clinical status was unknown until all graphic studies were tabulated An S_4 was demonstrated in 113 (73 1 per cent) of 152 individuals with and 68 (74 3 per cent) of 93 individuals without evidence of cardiovascular disease statistically an equal prevalence S_4 in older persons appears to be a normal phenomenon

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P wave changes on exercise in patients with isolated mitral stenosis

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It has been known since Einthoven[1] that exercise causes the P wave to increase in amplitude especially in Leads II and III[2-4] However changes in the frontal P vector following exercise have not been examined The P wave changes on exercise in the right precordial leads which indicates the horizontal vector of the P wave have been described in the literature except for the unpublished observations[5] cited by Sutnick and Soloff[6]

In this report, the P terminal forces (areas inscribed by terminal portions of P waves) in Leads V_{3R} V_1 and V_2 were observed before and after the exercise test, both in normal adults and in patients with mitral stenosis The aim of this paper is to describe changes of the P vector angle in the frontal and horizontal planes following exercise both in normal and in mitral stenosis patients

Material and methods

The control group (Cases 21 to 50) consisted of thirty normal subjects (15 men and 15 women) with no previous history of cardiopulmonary disease and with no abnormalities in physical examinations chest x rays and 12 lead electrocardiograms They were paramedical technicians, nurses and doctors of our hospital ranging in age from 18 to 30 years. As the single Master two step test appeared to constitute only mild exercise for the young workers the double Master two step test was performed on these control adults

A Fukuda 6 channel ECG recorder was used for ECG tracings. Following routine electrocardiographic procedures Leads I II, III V_{3R} V_1 and V_2 were recorded simultaneously at a paper speed of 50 mm per second. The sensitivity was increased to make a 1 millivolt calibration signal equal to 2 cm of deflection on the paper and accordingly the recording of the QRS complex was often truncated. The recorded P waves were large enough not to necessitate any magnifying lens for measurements of amplitude and duration

Immediately after the performance of the Master test on these 30 control adults Leads I II III V_{3R} V_1 and V_2 were recorded simultaneously again Before and after the double Master two step test pulse rate mean frontal P vector angle P wave amplitude in Lead II PQ interval and P terminal forces in Leads V_{3R} V_1 and V_2 were observed. ECG s before and after exercise were recorded with the patients in the supine position

The P terminal forces of right precordial leads (V_{3R} V_1 and V_2) were calculated as the algebraic product of the amplitude and duration of the terminal portion of the P wave as described by Morris and associates[7] who divided the P waves in V_1 into initial and terminal portions In our study only the terminal portion with the negative deflection was calculated The positive or isoelectric terminal portions of the P wave were presented as the zero terminal force in this paper

The duration of the terminal force was expressed as sec and the amplitude of the ter

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Table I P wave findings before and after exercise

	Before exercise	*After exercise*
CONTROL GROUP		
Pulse rate (beats per min)		
Male	67 3 ± 11 2	99 3 ± 17 2
Female	68 4 ± 8 4	105 5 ± 20 0
P wave amplitude in Lead II (mm)		
Male	1 11 ± 0 45	1 54 ± 0 65
Female	0 97 ± 0 27	1 43 ± 0 44
Frontal P wave vector angle (degrees)		
Male	53 6 ± 15 3	71 0 ± 10 5
Female	44 0 ± 13 5	63 3 ± 11 1
PATIENTS WITH MITRAL STENOSIS		
Pulse rate (beats per min)	69 0 ± 13 5	111 0 ± 14 2
P wave amplitude in Lead II (mm)	1 70 ± 0 65	2 32 ± 0 76
Frontal P wave vector angle (degrees)	51 0 ± 21 0	62 0 ± 17 0
P terminal force in Lead V_{3R} (mm sec)	−0 057 ± 0 052	−0 097 ± 0 078
P terminal force in Lead V_1 (mm sec)	−0 090 ± 0 065	−0 177 ± 0 113
P terminal force in Lead V_2 (mm sec)	−0 026 ± 0 044	−0 076 ± 0 097

The data are expressed as the mean plus or minus one standard deviation from the mean

minal force was described as 'mm which resulted in the dimension of mm sec of the terminal force The actual value of amplitude measurement of this study in which 1 mv presented 20 mm was divided by 2 to calculate the terminal force as 1 mv presented 10 mm in the previous examples in the literature [7,8]

The P wave configurations changed slightly with respiration To determine the duration or depth of the P terminal portion, five consecutive P wave tracings were measured and averaged The study group included 20 consecutive preoperative patients (Cases 1 to 20) with isolated mitral stenosis and with regular sinus rhythm Mitral insufficiency and other cardiac diseases were not observed in these cases

There were 6 men and 14 women 19 to 50 years of age with the average age at 33 years The single Master two step test was preferred in this group to the double Master two step test employed in the control group The method of ECG recordings was the same as in the previous group All 20 cases had mitral commissurotomy during admission The cardiac catheterizations were done preoperatively The pulmonary wedge pressure was recorded in all cases The correlation of the wedge pressure with the P terminal force at rest in V_1 was examined An estimate of functional capacity as classified by the criteria of the New York Heart Association was carried out Fifteen were included in Class II and five in Class III The single Master two step test could be carried out in 14 cases As the accomplishment of the single Master test was too difficult in the remaining six cases five of whom were included in Class III the single Master test was stopped on about half for them Patients too severely affected to perform even half of the single Master test were not included here

The exercise was completed in 1½ minutes All exercise tests were done by the same doctor (M Yokoyama)

Patients with mitral stenosis usually had unstable P waves The P wave configuration was apt to change abruptly A wandering pacemaker inside or outside the sinus node was quite common in this disease For strict comparison between pre and post exercise P wave configuration the location of the P wave origin should be identical for meaningful results Simultaneous 6 channel recordings of the P wave were found to be useful for recognizing an abrupt change in the P wave origin A long strip of ECG recording was also needed for its detection Following exer

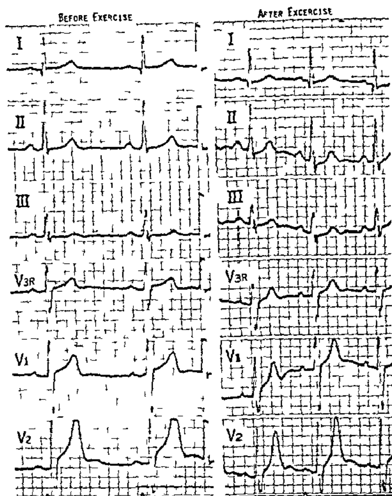


Fig 1 Case 26 (control group) 25 year old man On exercise pulse rate increased 60 to 96 per minute P wave amplitude in Lead II increased from 1 0 mm to 1 5 mm Mean frontal P vector angle in degrees changed from +60 degrees to +75 degrees. PQ interval shortened from 0 17 to 0 15 sec Negative P terminal forces could not be observed before and after exercise in Leads V_{3R} V_1 and V_2 Elapsed time in seconds is shown at the bottom

cise continuous 2 minute recordings were performed routinely with a short strip of 5 minute post exercise recording

In two cases the origin of the P wave was completely altered for several minutes following exercise and in one case the P waves were deeply negative in Leads II III and aV_F on resting ECG suggesting coronary sinus rhythm or atypical sinus origin The three above mentioned cases were not included in the 20 cases which composed the study group

Results

Measurements of the P wave in 30 control cases were described in Table I The amplitude of the P wave in Lead II increased from approximately 1 0 mm to 1 5 mm following the double Master two step test The mean frontal P vector became vertical following exercise changing from about +50 degrees to +65 degrees There were no cases in which the mean frontal P vector angle in degrees decreased following exercise Only in one control (Case 33) was the P vector angle unchanged by exercise The P negativity in Lead V_{3R} of the control group was found in 4 cases out of 30 before exercise Following the double Master two step test in these four cases the P terminal force was unaltered. The values were all within −0 010 mm sec The other 26 cases did not show a negative P terminal force before and after exercise in Lead V_{3R}

In Lead V_1 of the control 7 cases showed a

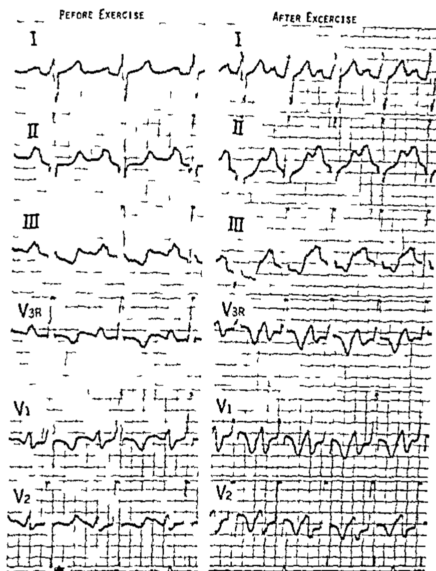


Fig 2 Case 18 (mitral stenosis) 19 year old man On exercise pulse rate increased from 87 to 105 per minute P wave amplitude in Lead II increased from 2 0 to 3 0 mm Mean frontal P vector angle (80 degrees) remained unchanged before and after exercise PQ interval shortened from 0 18 to 0 16 sec Negative P terminal forces in V_{3R} V_1 and V_2 were 0 0 040 0 020 mm sec respectively before exercise They increased markedly to 0 090 0 280 0 210 mm sec respectively following exercise

negative P terminal force after the exercise The other 23 cases did not show any negative P terminal force before and following the double Master two step test The values of the force were all within −0 020 mm sec (Fig 1)

In Lead V_2 of the control group there were no cases showing a P negativity before and after exercise

For the analysis of the P waves in patients with mitral stenosis, men and women patients were not divided, but were collected altogether

The pulmonary wedge pressure was 18 0 ± 6 2 mm *Hg The correlation with the wedge pressure* and the P terminal force at rest in V_1 was *not detected*

Pulse rate was 69 0 per minute at rest which changed to 111 0 per minute following exercise This rate of increase was similar to the control cases who performed the double Master two step test (Table I)

The P wave amplitude in Lead II was 1 70 mm which was significantly higher than in the control group Following exercise the amplitude increased to 2 32 mm

Four cases out of 20 in the mitral stenosis group showed P waves higher than 2 5 mm in Lead II in the resting ECG Following exercise 6 cases out of 20 showed P wave amplitude higher than 2 5 mm The atrial vector angle in the frontal plane changed from +51 degrees to +62 degrees It was interesting to note that these frontal P vector angles in degrees in the mitral

stenosis group were almost equivalent to those of the control group both in pre and post exercise conditions. The left atrial enlargement or hypertrophy does not induce the decrease of the mean P frontal vector angle in degrees

By exercise the frontal P vector became more vertical or unchanged. In 5 cases out of 20 in the mitral stenosis group the frontal P vector angle did not change In the other 15 cases the P vector angle changed to some extent becoming more vertical No cases were found in which the P vector angle decreased in degrees

In Lead V_{3R} of the study group the negative P terminal force changed from −0 057 to −0 097 mm sec At rest 4 out of 20 cases showed no negative P terminal force Following exercise only one case did not show a negative terminal force The other 19 cases showed a negative terminal force after exercise

In Lead V_1 where the P negativity was usually most prominent, all 20 cases showed to some extent the negative P terminal force at rest It was −0 090 mm. sec before exercise increasing to −0 177 mm sec. following exercise (Fig 2)

In Lead V_2 of the study group the P terminal force changed from −0 026 to −0 076 mm sec on exercise Before exercise 11 cases out of 20 showed P negativity but the remaining 9 cases did not show any negativity Following exercise the P negativity was found in 17 cases Only three cases demonstrated no P negative area

The P negativity of the study group was prominent in Lead V_1 next Leads V_{3R} and V_2 respectively

Discussion

The increase of the P wave amplitude in Leads II and III on exercise have been reported previously Irisawa and Seyama[4] suggested that it was induced by the synchronization of bilateral atrial excitation In our experience however the P wave amplitude in Lead II often increased by more than double on exercise The P wave amplitude in Lead I always decreased on exercise Therefore these P wave changes could be interpreted as a tendency of the P vector to become more vertical

Recently Bruce and associates[9] reported increase in the spatial magnitude of P but no significant change in the vector angle observed after exercise in normal young adults

The second portion of the P wave in the surface electrocardiogram has been shown to represent electrical depolarization of the left atrium alone[10-12] In normal subjects the vector from the second portion of the P wave is most nearly perpendicular to the axis of V_1 and, therefore little deflection is inscribed. With left sided valvular lesions Sano and colleagues[13] have shown that the vector from the second half of the P wave rotates posteriorly in the horizontal plane With this rotation the second portion of the P wave in V_1 takes a deep negative deflection

In the esophagograms in cases with mitral stenosis the esophagus was displaced posteriorly by the posterior enlargement of left atrium Actual anatomical positional changes of the left atrium seemed to correlate with the posterior displacement of the atrial vector in the horizontal plane

Kasser and Kennedy[14] reported that the V_1 terminal force showed a highly significant correlation with changes in left atrial volume but related less well to increase in left atrial pressure

The further increase of the P negativity in the right precordial leads following exercise could be explained by further distension of the left atrium

We had performed similar research on patients with aortic insufficiency or atrial septal defect, or pulmonary stenosis. The increase of negative deflection in the right precordial P waves following exercise were very mild compared with those found in patients with mitral stenosis This could be attributed to the ease with which the left atrial pressure increases and to subsequent left atrial dilation in cases with mitral stenosis

Sutnick and Soloff[8] have reported posterior rotation of the atrial vector during acute left ventricular failure Such rotation has also been found in acute myocardial infarction[15] We insist, however that the increase of the P wave negativity in V_1 on exercise is not always related to the appearance of cardiac failure The phenomenon should be simply understood as the posterior rotation of the horizontal P vector

The P negativity in the right precordial leads was usually unchanged following the mitral commissurotomy The postoperative exercise test however rarely induced the increase of P negativity in the right precordial leads which we will report on another occasion

Summary

Patients with mitral stenosis usually showed a marked increase in the P negativity following exercise The P terminal force in Lead V_1 in 20 cases with isolated mitral stenosis was −0 090 mm sec before exercise, which changed to −0 177 mm sec following the single Master two step test

Normal adults never showed such changes on exercise The phenomenon was considered to be due to the posterior rotation of the P wave vector in the horizontal plane, which was induced by the enlargement of the left atrial wall on exercise

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Adrenalıne-ınduced lıgnocaıne resıstant dysrhythmıas ın experımental myocardıal ınfarctıon

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Ischemıc heart dısease ıs the major cause of premature cardıac death Sıxty one per cent of deaths from myocardıal ınfarctıon among ın dıvıduals less than 65 are sudden ın that they occur wıthın one hour of the onset.[1] Ventrıcular fıbrıllatıon ıs the cause of more than 90 per cent of these early deaths [2,3]

It has been stated that sınce prımary ventrıcu lar fıbrıllatıon dıd not develop ın hospıtalızed pa tıents wıth acute myocardıal ınfarctıon ın whom ventrıcular dysrhythmıas were treated wıth lıg nocaıne the drug should be gıven to patıents at the ınceptıon of the coronary attack and prıor to transport to hospıtal [4] However experıence of the pre hospıtal phase of acute myocardıal ın farctıon ındıcates that lıgnocaıne ıs less effectıve ın the control of the ventrıcular dysrhythmıas occurrıng wıthın two hours of the onset of symptoms than those occurrıng later [5,6] Prac tolol often ıs effectıve ın controllıng the dysrhythmıas whıch occur ın the early phase but not ın the late phase of acute myocardıal ın farctıon [7] As practolol abolıshes arrhythmıas through blockade of beta adrenoceptors an ın crease ın blood or tıssue levels of catecholamınes may be an ımportant factor ın producıng these arrhythmıas.[5,7] Thıs proposıtıon ıs supported by the observatıon that 46 per cent of patıents seen wıthın 30 mınutes of the onset of acute myocar dıal ınfarctıon show clınıcal evıdence of sym pathetıc overactıvıty [8]

In vıew of the overwhelmıng ımportance of determınıng the most effectıve regıme for con trol of the lethal early ventrıcular dysrhythmıas of acute myocardıal ınfarctıon ın whıch cate cholamıne release may play a part, a study has been made of the effects of antıdysrhythmıc agents on the ventrıcular dysrhythmıas pro duced by the admınıstratıon of adrenalıne after lıgatıon of a coronary artery ın dogs [9] In thıs paper we descrıbe the effects of lıgnocaıne on these dysrhythmıas

Methods

Observatıons of the effects of adrenalıne on conscıous dogs were made 3 to 4 days after lıga tıon of a coronary artery

The studıes were made on 11 greyhounds weıghıng 20 to 35 kılograms. The dogs were anesthetızed by the ıntravenous admınıstratıon of methohexıtone 10 mg per kılogram of body weıght and were respıred through a cuffed en dotracheal tube wıth room aır and halothane (0 5 to 2 0 per cent) Under aseptıc condıtıons the heart was exposed through the fıfth left ınter costal space [10,11] Two lıgatures were placed around the anterıor descendıng branch of the left coronary artery at a level 1 to 2 cm dıstal to the tıp of the left atrıal appendage or ım medıately dıstal to the second major branch of thıs artery to the anterıor surface of the left ventrıcle The artery was then occluded ın two

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Table I Effects of the repeated intravenous administration of adrenaline (10 μg/Kg) on cardiac rhythm and mean arterial pressure in 3 conscious dogs 3 to 4 days after coronary artery ligation

Dose of adrenaline		*1st*	*2nd*	*3rd*	*4th*	*5th*	*6th*	*7th*
Maximum ectopic rate (beats per min) after adrenaline		257 ± 22†	243 ± 19	235 ± 25	219 ± 21	211 ± 26	213 ± 31	217 ± 33
Ectopic beats in 3 min after adrenaline		614 ± 68	613 ± 70	580 ± 93	574 ± 80	560 ± 94	541 ± 101	535 ± 106
Mean arterial pressure (mm Hg)	2 minutes before adrenaline	102 ± 6	107 ± 6	106 ± 4	94 ± 9	97 ± 3	101 ± 4	102 ± 5
	Maximum response to adrenaline	263 ± 26	259 ± 17	242 ± 10	229 ± 17	239 ± 9	234 ± 7	235 ± 5

P< 0 05 of values of first two doses of adrenaline
†Values are the mean ± S E M

stages[12] The first ligature was tied around the artery and a 21 gauge needle The needle was then removed leaving a partial occlusion of the artery The chest was closed in layers and the animals were allowed to recover

The observations on the conscious animals were made on the third or fourth postoperative day Arterial pressure was recorded from a polythene catheter (Portex) inserted into the femoral artery under local anesthesia and attached to a pressure transducer (Consolidated Electrodynamics Type 4 327 L221) Arterial pressure (phasic or electronic mean) and the electrocardiogram (Leads II and aV_1) were recorded continuously on a Devices M4 recorder Drugs were administered through a cannula in a peripheral vein usually the femoral

The experimental procedure was not completed in 2 of 11 dogs in one because of the development of hemothorax and in the other because ventricular fibrillation occurred after two doses of adrenaline

Seven doses of adrenaline 10 μg per kilogram of body weight were given intravenously to the remaining 9 dogs at 10 minute intervals After two injections of adrenaline had been given 6 dogs received increasing doses of lignocaine (0 5 to 8 0 mg per kilogram of body weight) intravenously at 10 minute intervals each dose of lignocaine was given 2 minutes before the administration of the next challenge dose of adrenaline Three randomly selected dogs only received repeated doses of adrenaline and are referred to as the control group

The electrocardiogram was recorded continuously throughout a control period and during the administration of drugs. The ectopic and sinus beats in each 30 second period after the administration of adrenaline were counted from the continuous records of the electrocardiogram Sinus beats were defined as those of normal mean frontal QRS vector preceded by a P wave All other complexes were denoted as ectopic[9] The great majority of these ectopic beats were ventricular in type but on some occasions short bursts of rapid supraventricular dysrhythmias occurred The total number of ectopic beats in the 3 minute period after the administration of adrenaline and the maximum ectopic rate defined as the greatest number of ectopic beats in any 30 second period (expressed as rate per minute) were determined after the administration of each dose of adrenaline Statistical significance of the results was assessed by analyses of variance

At the conclusion of each experiment the dog was killed by the intravenous administration of sodium pentobarbitone and the heart was removed The presence of a myocardial infarction in the antero apical area of the left ventricle was confirmed by gross examination of the heart in all the animals and by histological examination in one The arterial obstructions were demonstrated on all the hearts by perfusing the coronary arteries with heparinized saline and a barium sulphate suspension

The following drugs were used (—) adrenaline bitartrate (C Zimmerman and Co) lignocaine

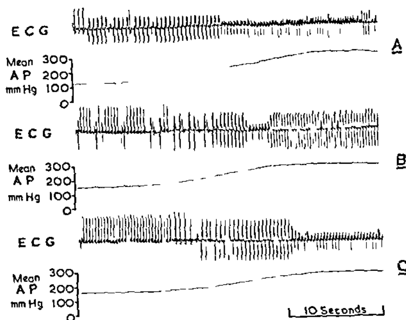


Fig 1 A through C Each pair of tracings (A B and C) shows synchronous records of the production of ventricular tachycardia and a rise in mean arterial blood pressure (*Mean A P*) by the repeated intravenous administration of single doses of adrenaline (10 µg per kilogram of body weight) to a dog 4 days after ligation of the anterior descending branch of the left coronary artery The adrenaline was injected 15 seconds prior to the start of the traces shown *Panel A* No lignocaine The ventricular tachycardia lasted for 2 minutes. *Panel B*, 2 minutes after the administration of lignocaine 4 mg per kilogram of body weight Ventricular tachycardia persisted for 2 minutes. *Panel C* 2 minutes after the administration of lignocaine 8 mg per kilogram of body weight Spontaneous ectopic activity was suppressed but ventricular tachycardia was not prevented.

hydrochloride (Xylocaine Astra Hewlett) and methohexitone sodium (Brietal Parke Davis) Drugs were freshly dissolved at the required concentration in solution of 0 9 per cent sodium chloride doses are expressed in terms of the salt Halothane (Fluothane I C I Pharmaceuticals) was administered from a Blease Universal anesthetic vaporizer

Results

Control observations The responses to a series of 7 doses of adrenaline 10 µg per kilogram of body weight given to 3 dogs which did not receive lignocaine are shown in Table I There was a tendency for the maximum ectopic rate the total number of ectopic beats, and the maximum arterial pressure after the administration of adrenaline to decrease with successive doses of adrenaline The maximum ectopic rate and the total number of ectopic beats in the first 3 minutes after adrenaline were significantly less ($p < 0.05$) after the fifth sixth and seventh doses of adrenaline in comparison to the responses after the first two doses.

Effect of lignocaine Some results from one experiment are shown in Fig 1 Before the administration of any drugs frequent ventricular ectopic beats were present The intravenous administration of adrenaline 10 µg per kilogram of body weight produced a large increase in arterial pressure and a rapid ventricular tachycardia Similar effects were observed following the administration of adrenaline two minutes after the intravenous injection of lignocaine (0 5 1 0 2 0 and 4 0 mg per kilogram of body weight) The administration of lignocaine 8 0 mg per kilogram of body weight abolished the spontaneous ventricular ectopic beats and produced sinus rhythm but did not alter the responses to adrenaline

Similar results were obtained in the 5 other dogs (Table II) After the intravenous administration of lignocaine (4 to 8 mg per kilogram of body weight) the spontaneously occurring ventricular ectopic beats were abolished. However in no case did lignocaine prevent the dysrhythmic effects of the subsequent administration of adrenaline although it caused a

Table II The effects of the intravenous administration of increasing doses of lignocaine on the changes in cardiac rhythm and mean arterial pressure produced by the repeated intravenous administration of adrenaline, 10 μg/Kg of body weight to 6 dogs after coronary artery ligation

Dose of lignocaine (mg / Kg)		*0*	*0*	*0 5*	*1 0*	*2 0*	*4 0*	*8 0*
Max ectopic rate (beats per min) after adrenaline		236 ± 16	239 ± 14	226 ± 14	215 ± 11	207 ± 12*	196 ± 10†	172 ± 12† (n=5)
Ectopic beats in 3 min after adrenaline		574 ± 51	576 ± 43	569 ± 47	534 ± 46	476 ± 43*	380 ± 59†	261 ± 60†
Mean arterial pressure (mm Hg)	2 minutes before adrenaline	102 ± 5	110 ± 11	109 ± 11	104 ± 9	104 ± 10	98 ± 9	101 ± 11 (n=6)
	Maximum response to adrenaline	255 ± 19	256 ± 22	234 ± 12	242 ± 14	238 ± 14	237 ± 13	236 ± 17 (n=5)

P < 0 05
†P < 0 01 of values for first two doses of adrenaline

progressive and significant reduction in the severity of the dysrhythmia indicated by reductions in the maximum ectopic rate and in the total number of ectopic beats (Table II) As there was a reduction in the dysrhythmic response to adrenaline in both control and lignocaine groups of dogs only differences between the control and treated groups are of importance The highest dose of lignocaine 8 mg per kilogram of body weight significantly reduced the total number of ectopic beats in the 3 minute period after the administration of adrenaline as compared with the response to the seventh dose of adrenaline in the dogs given no lignocaine (F = 6 38, p < 0 05) The maximum frequency of ectopic beats in the dogs given 8 mg per kilogram of body weight lignocaine was not significantly different from that in the dogs which did not receive lignocaine With one exception the administration of lignocaine did not affect resting arterial pressure or the increase in arterial pressure in response to adrenaline One dog died from hypotension after the administration of the largest dose of lignocaine and before the administration of adrenaline Doses of lignocaine greater than 8 0 mg per kilogram of body weight were not used because of the reported toxic neurological effects of dosage in this range [11]

Discussion

The present results indicate that lignocaine (0 5 to 8 0 mg per kilogram of body weight) does not prevent the dysrhythmias produced by the administration of adrenaline 10 μg per kilogram of body weight, to dogs 3 to 4 days after coronary artery ligation Although the total number of ectopic beats in the 3 minute period after the administration of adrenaline was significantly less in the dogs which received lignocaine 8 mg per kilogram of body weight than in those which did not the maximum frequency of ventricular ectopic beats was similar in both groups The relevance of this difference in the effects of lignocaine on the two measurements is not clear The largest dose of lignocaine used in these experiments 8 mg per kilogram of body weight, as a single intravenous injection is 4 to 5 times larger than the dose of lignocaine used in the clinical situation The administration of the larger doses of lignocaine 4 and 8 mg per kilogram of body weight, produced concentrations in peripheral venous blood of 3 8 and 7 8 μg per millilitre, respectively in one dog in which they were determined at the time of onset of adrenaline dysrhythmia The latter blood concentration is greater than the blood levels (1 2 to 6 0 μg per millilitre) associated with abolition of cardiac dysrhythmias in patients [13]

The present experiments differ from the clinical situation Major differences include the use of a thoracotomy the otherwise healthy canine heart the large doses of adrenaline used and the marked increase in arterial pressure associated with the development of the dysrhythmia

The dogs were studied 3 to 4 days after coronary artery ligation but in man increased blood concentration of catecholamines[14] occur within 24 hours of myocardial infarction

The beta adrenoceptor blocking drugs practolol (1 mg per kilogram of body weight) and propranolol (1 mg per kilogram of body weight) greatly reduced or prevented the dysrhythmia produced by the administration of adrenaline 10 μg per kilogram of body weight in dogs 3 to 4 days after coronary artery ligation [10,15] These effects of propranolol and practolol are due to beta adrenoceptor blockade as the dextro isomer of propranolol was much less effective in abolishing the dysrhythmia [10] Thus the relative ineffectiveness of lignocaine in the present experiments is due to the absence of beta adrenoceptor blocking properties which appear to be essential for abolition of these dysrhythmias induced by increased sympathetic activity

The beneficial effects of practolol observed clinically are associated with blood concentrations of less than 1 μg per millilitre [7] At this concentration practolol does not reduce the rate of rise of the action potential of the rabbit atria [16] Hence the effects of practolol in patients must be attributed to specific beta adrenoceptor blockade As practolol is effective and lignocaine ineffective in abolishing adrenaline induced dysrhythmias in dogs after coronary artery ligation and as practolol often abolishes lignocaine resistant ventricular dysrhythmias in the early phase of acute myocardial infarction in man [7] excessive circulating and neuronal catecholamines may play an important role in the production and maintenance of these dysrhythmias in man

The present observations provide further evidence to indicate that lignocaine may not be the drug of choice in treating ventricular dysrhythmias in the early stage of acute myocardial infarction when there is increased sympathetic activity

Dr J G Kelly determined the blood levels of lignocaine [17] We are also indebted to Mr J Collins and Mr W Leahey for technical assistance and to Astra Hewlett Ltd. for the gift of lignocaine

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Overriding right atrioventricular valve in association with mitral atresia

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In most of the reported cases of mitral atresia the atrial and ventricular septa were adjoined at the base of the ventricles and pulmonary venous blood reached the usually hypoplastic left ventricle only via the right ventricle and a ventricular septal defect (VSD)[1-4] However, in a recent case,[5,6] the atrial and ventricular septa did not meet at the base of the ventricles and the right atrioventricular (AV) valve overrode the ventricular septum so that blood from the right atrium entered both right and left ventricles directly

A review of 23 specimens of mitral atresia in the pathology collection of the Johns Hopkins Hospital revealed three additional examples of overriding right AV valve These three specimens and the above mentioned specimen of Navarro Lopez and associates[5,6] each had appropriately sized ventricles and no ventricular outflow stenosis or atresia features that theoretically make this combination of anomalies amenable to corrective surgery



Fig 1A Case 1 mitral atresia overriding right atrioventricular valve and ventricular septal defect (VSD) Cineangiogram frame with catheter across foramen ovale Although left atrium (*LA*) and appendage (*LAA*) are outlined and contrast can be seen to spill along catheter (*arrows*) into right atrium (*RA*) this angiogram was misinterpreted as showing mitral stenosis rather than atresia

Case reports

Case 1 This female infant was born by cesarean section to a diabetic mother at 37 weeks of gestation The birth weight was 2 7 kilograms Mild cyanosis appeared at two days of age Examination at 11 days of age revealed normal pulses and pressures an ejection systolic murmur along the left sternal border that ended before the split second sound and an accentuated pulmonary component The electrocardiogram (ECG) showed an indeterminate axis with a suggestion of biventricular hypertrophy The chest radiograph revealed an enlarged heart and increased pulmonary vascularity of the arterial type

At cardiac catheterization an increase in oxygen saturation was noted at the right atrial level (72 per cent with vena cava saturations of 54 and 52 per cent) with a further increase in the pulmonary artery (76 per cent) An aortic root injection ruled out a patent ductus arteriosus The catheter passed from the right atrium through an atrial communication into the left atrium where the pressure was elevated to 16 mm Hg A cineangiogram showed contrast material outlining the appendage and body of the left atrium (Fig 1*A*) but the subsequent rapid appearance of contrast in the left ventricle was interpreted as indicating mitral stenosis rather than mitral atresia The left ventricle was entered from the right atrium but it was presumed from withdrawal tracings that the catheter had first traversed the right ventricle and a VSD A left ventricular angiocardiogram (Fig 1*B* and *C*) showed an adequate left ventricular cavity and a VSD of moderate size After the catheterization vigorous medical treatment partially

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Fig 1B and 1C Mitral atresia overriding right AV valve and VSD Retrograde left ventricular angiogram An teroposterior (B) and lateral (C) views illustrate normal relation of great vessels Contrast crosses VSD into right ventricular outflow tract (RV INF) the right atrium (*RA*) also opacifies *LV* = left ventricle *RPA MPA* and *LPA* = right main, and left pulmonary arteries *AO* = aorta.

relieved the congestive failure and the infant s progress in a convalescent hospital seemed satisfactory until she died suddenly at nine weeks during an apneic spell

Description of the heart. The small left atrium d monstrated a thickened endocardium a normal appendage normal entrance of the pulmonary veins, absent mitral orifice (Fig 2A) and a single exit consisting of a patent foramen ovale which measured 6 mm in diameter when the valve was stretched to its open position The large right atrium received the venae cavae and coronary sinus in a normal manner The right AV valve measured 1 3 cm in diameter and opened into both right and left ventricles straddling the ventricular septum (Fig 2B) Chordae tendineae from this valve were attached to papillary muscles of both right and left ventricles The VSD was 1 0 cm in diameter at its widest point above the crest of the ventricular septum and was bounded by the leaflets of the overriding right AV valve which were attached to the crest of the septum in a manner resembling the anatomy seen in AV canal defect (Fig 2B and D) The ventricles were of appropriate size and shape each measuring 3 8 cm from the AV valve ring to the apex The outflow portion of the right ventricle demonstrated a normal infundibulum the pulmonic valve was 0 8 cm in diameter (Fig 2C) The left ventricular outflow tract resembled that seen in AV canal defect (Fig 2D) it was not obstructed. The aortic valve measured 0 8 cm in diameter the coronary ostia were normal A diverticulum of the aorta at the site of the closed ductus arteriosus was 0.2 cm long

Case 2. This male infant was born after an uncomplicated pregnancy labor and delivery weighing 4 4 kilograms but developed progressive cyanosis, tachypnea and cough during the first week of life Examination at 14 days of age revealed normal pulses and pressures a harsh pansystolic murmur and thrill along the left sternal border and a single second sound. An ECG showed left ventricular predominance The chest radiograph showed an enlarged heart and increased arterial and venous markings in the lung fields At cardiac catheterization systemic pressure was measured in the right ventricle (110/0/6 with a pressure of 100/0/11 in the left ventricle) which led to the transposed aorta The catheter was believed to enter the left ventricle via an atrial septal defect and mitral valve A left ventricular cineangiogram revealed a VSD with a left to right shunt that opacified an appropriately sized right ventricle (Fig 3) The catheter was maneuvered into the left atrium but it was not recognized as a small chamber with absent mitral valve partially because a cineangiogram there did not outline the atrial septum and the contrast material rapidly opacified the left ventricle The decision to perform a Blalock Hanlon atrioseptectomy and pulmonary artery banding was based upon the belief that the patient had transposition of the great vessels with a VSD Surgery resulted in dramatic improvement but by 20 months of age the child exhibited marked cyanosis and clubbing He died at home at 25 months of age

Description of the heart. Examination of the small left atrium revealed a normal appendage and entrance of the pulmonary veins and an absent mitral orifice (Fig 4A) The Blalock Hanlon atrial septal defect was 1 3 cm in diameter The large right atrium received the venae cavae and coronary sinus in a normal fashion The right AV valve measured 2 0 cm in diameter and opened into both right and left ventricles straddling the ventricular septum (Fig 4B) Chordae tendineae from this valve inserted into papillary muscles of both ventricles. The diameter of the VSD was 1 4 cm at its widest point above the crest of the ventricular septum It was bounded by the leaflets of the overriding right AV valve which were attached to the crest of the septum in a manner resembling the anatomy seen in AV canal defect (Fig 4C) The normal right ventricle measured 4 6 cm from valve ring to apex its normal outflow tract led to a normal aortic valve measuring 1 4 cm in diameter (Fig 4C) The right and left coronary ostia were in the usual position for



Fig 2 A through D Heart specimen in Case 1 A View of left atrium (*LA*) showing thickened endocardium Arrow points to exit at foramen ovale (5 mm in diameter) *LPV* = left pulmonary vein *A* = tip of left atrial appendage B Posterior view of right atrium (*RA*) showing sectioned ventricular septum (*VS*) and anterior and posterior attachments (*arrows*) of overriding right atrioventricular valve (*RAVV*) to crest of ventricular septum *LV* = left ventricle *RV* = right ventricle C Anterior view of right ventricle (*RV*) illustrating normal outflow tract *MPA* = main pulmonary artery *PB* and *SB* = parietal and septal bands of crista supraventricularis. D View of left ventricle (*LV*) showing typical smooth walled septum and a portion of overriding right atrioventricular valve (*RAVV*) *LAA* = left atrial appendage *rcc ncc* and *lcc* = right non and left coronary cusps of aortic valve

transposition The left ventricle (4 2 cm from valve ring to apex) contained a single posterolateral papillary muscle The posterior left ventricular outflow tract was unobstructed and led to a normal pulmonary valve (1 5 cm in diameter) The pulmonary artery band did not interfere with valve function but the pinpoint orifice at the level of the band led to a dilated main pulmonary artery The ductus arteriosus was probe patent

Case 3 This severely cyanotic and syncopal two month old female infant had an emergency end to side anastomosis of the right subclavian artery to the right pulmonary artery (Blalock Taussig anastomosis) which was carried to completion despite the finding at operation of a large distended right pulmonary artery The infant died in the postoperative period without regaining consciousness. Additional clinical information is unavailable

Description of the heart The small left atrium had a thickened endocardium normal appendage and entrance of the pulmonary veins absent mitral orifice (Fig 5*A*) and a single exit consisting of a patent foramen ovale which

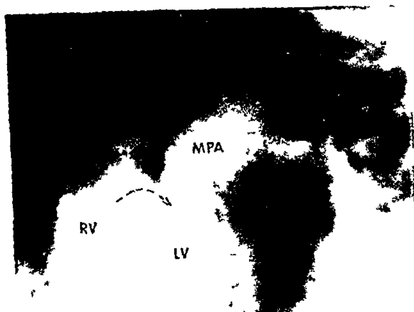


Fig 3 Case 2 mitral atresia overriding right atrioventricular valve and VSD associated with transposition of the great vessels Cineangiogram frame with retrograde catheter passed across aortic valve into right ventricle (*RV*) Contrast is shunting across a ventricular septal defect (*dotted arrow*) into the dilated left ventricle (*LV*) outlining the ventricular septum *MPA* = main pulmonary artery

measured 2 mm at its widest point The large right atrium received the venae cavae and coronary sinus in a normal manner The right AV valve measured 2 6 cm in diameter and opened into both left and right ventricles straddling the ventricular septum (Fig 5*B*) Chordae tendineae from this valve inserted into papillary muscles in both ventricles The VSD was 7 mm in its widest dimension being bounded on the apical side by the crest of the ventricular septum and on the other sides by the leaflets of the overriding right AV valve (Fig 5*B*) The normal right ventricle measured 3 1 cm from AV orifice to apex. The infundibulum led to a normal aortic valve 0 8 cm in diameter (Fig 5*C*) with the right and left coronary ostia in the usual position for transposition. The left ventricle measured 3 7 cm. from base to apex The posterior left ventricular outflow tract was unobstructed and led to a normal pulmonary valve (0 8 cm in diameter) and a dilated pulmonary artery (Fig 5*D*) The Blalock Taussig anastomosis was patent

Discussion

In the reported cases of mitral atresia [1-4] survival beyond the age of one year is unusual patients who do survive for more than a year usually have transposed great vessels which may protect the pulmonary vascular bed from excessive pressure and flow in infancy They also have an adequate communication between left and right atria which prevents hypoxia Third, survival requires an unobstructed flow of blood from the right ventricle directly to the aorta from the right ventricle to the aorta via a large VSD or from a single ventricle to the aorta To survive beyond infancy it is not necessary for the patient to have two normally sized ventricles

The patient reported by Navarro Lopez and colleagues[5,6] survived to the age of 11 years with two normally sized ventricles and a normal arrangement of the great vessels The pulmonary veins returned to a left atrium whose only outlet was the right atrium via a narrow ostium primum atrial septal defect which eventually was partially occluded by an organizing left atrial thrombus Anatomy similar to that of the right AV valve has been reported previously in cases of straddling or overriding AV valve VSD of the AV canal type [7-9] and variants of double inlet or single ventricle [10-13] The anatomy in our Case 1 was similar to that in the case of Navarro Lopez and associates [5,6] but the patient died in infancy in an apneic spell with pulmonary arterial and venous hypertension The patient in our Case 2 survived to the age of two years with his lungs protected by a Blalock Hanlon atrioseptectomy and a banding of the transposed pulmonary artery but succumbed probably because as he grew the band did not allow a pulmonary blood flow adequate to his size

The three cases reported here and the case of Navarro Lopez and colleagues[5,6] differ from the



Fig 4 A through C Heart specimen in Case 2 A View of left atrium (*LA*) Arrow points to opening into left atrial appendage *LPV* = left pulmonary vein B Posterior view of large right atrium (*RA*) showing overriding right atrioventricular valve (*RA VV*) which is attached by chordae tendineae (*arrows*) to crest of ventricular septum (*VS*) Blalock Hanlon atrial septal defect (*ASD*) measures 1 2 cm in diameter *LV* = left ventricle *RV* = right ventricle C Anterior view of right ventricle showing aortic valve supported by parietal (*PB*) and septal (*SB*) components of the crista supraventricularis *PM* = lateral papillary muscle *rcc* and *lcc* = right and left coronary cusps of aortic valve

usual cases of mitral atresia[1-4] in that the atrial and ventricular septa do not adjoin each other at the atrioventricular junction thus allowing the right AV valve to override the ventricular septum In all four cases there were appropriately sized left ventricles and absence of ventricular outflow stenosis or atresia features that *theoretically* make this combination of anomalies amenable to total correction However, corrective surgery should be considered only after a precise diagnosis has been made Angiography is invaluable here a left atrial injection will outline features diagnostic of mitral atresia (Fig 1*A*) especially when the result is combined with satisfactory pullback recordings and oximetry readings The overriding nature of the right AV valve the size of the ventricles the VSD and the outflow tracts may be studied in cineangiograms or biplane left ventriculograms (Figs 1*B* and *C* 3*A*)

The management of a patient with mitral atresia overriding right AV valve and VSD depends upon his symptoms Obviously a patient who presents with minimal cyanosis and without



Fig 5 A through D Heart specimen in Case 3 A View of opened left atrium (*LA*) showing thickened endocardium and absence of mitral valve Arrow points to 2 mm opening in foramen ovale *LPV* and *RPV* = left and right pulmonary veins B Posterior view of large right atrium showing right atrioventricular valve (*RAVV*) straddling the ventricular septum and attached by chordae tendineae (*arrows*) to its crest *LV* = left ventricle *RV* = right ventricle C Anterior view of right ventricle showing parietal (*PB*) band of crista supraventricularis below normal aortic valve *pm* = papillary muscle *RAVV* = right atrioventricular valve *rcc* and *lcc* = right and left coronary cusps of aortic valve *SB* = septal band D View of opened left ventricle showing fibrous continuity between right artrioventricular valve and pulmonary valve *LAA* = left atrial appendage *MPA* = main pulmonary artery

excessive pulmonary blood flow should be treated conservatively If pulmonary blood flow is excessive pulmonary artery banding may be helpful As in the more usual cases of mitral atresia, pulmonary venous hypertension should be relieved by atrioseptectomy only if the pulmonary vascular bed is protected by surgical banding or pulmonary stenosis Whether corrective surgery would be successful is speculative and it should be considered only after a precise diagnosis has been made As suggested by Navarro Lopez and associates[5] it may be possible to place an artificial valve between the left atrium and ventricle Another possible surgical approach is to excise the atrial septum and convert the resulting single atrium and the right AV valve into two atrial chambers and valves with a repair similar to that used for common AV canal[14,15] When transposition of the great vessels is also present, it may be possible to appropriately compartmentalize the combined atrial chamber as in the Mustard procedure

Summary

Three cases of mitral atresia with overriding right atrioventricular valve ventricular septal defect and normally sized left ventricle are reported two of them with transposition of the great vessels Although the combination of anomalies is rare the possibility that palliative and/or corrective surgery could be accomplished indicates that in suspected cases of mitral atresia diagnostic efforts aimed at accurate delineation of the associated defects must be made

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Renal functıon studıes ın hyponatremıc cardıac patıents wıth edema (dılutıon syndrome)

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Several years ago Merrıll[1] showed that renal plasma flow and glomerular filtratıon rate were reduced ın patıents wıth heart faılure and sug gested that the ıncreased salt and water reten tıon mıght be due to more complete tubular reabsorptıon of the dımınıshed filtered load of sodıum Another theory[1 4] has been based on the common findıng of a dısproportıonate reductıon ın effectıve renal blood flow and glomerular filtratıon rate ın patıents wıth heart dısease an effect whıch has been attrıbuted to a greater degree of constrıctıon of the efferent arterıoles The ratıo between glomerular filtratıon rate and renal plasma flow—ı e the filtratıon fractıon—ıs therefore frequently found abnormally ele vated. As essentıally no proteın ıs filtered through the glomerulı an elevated filtratıon fractıon results ın an ıncreased postglomerular colloıd osmotıc pressure The resultant ıncreased gradıent from the renal tubular lumen to the perıtubular capıllarıes ıs assumed to exert an osmotıc force favorıng water reabsorptıon wıth sodıum movıng passıvely to maıntaın ısotonıcıty

Prevıous studıes ın thıs field have maınly ın cluded patıents free from overt evıdence of con gestıve heart faılure In the followıng study we have studıed the hemodynamıc and renal systemıc alteratıons ın a selected group of 8 pa tıents beıng characterızed by marked edema hyponatremıa and ın most cases ıncreased total body sodıum (dılutıon syndrome) Applyıng the New York Heart Assocıatıon Classıficatıon at the tıme of the study all patıents were ın Class IV

Methods

The patıents had aortıc or mıtral valvular or coronary heart dısease They had all been takıng dıgıtalıs and dıuretıcs for several months prıor to admıssıon and thıs treatment was contınued up to the tıme of study Age and sex dıstrıbutıon as well as pertınent laboratory data are shown ın Table I All patıents examıned had fluıd and electrolyte dısturbances and clınıcal and laboratory evaluatıon enabled us to dıstınguısh most of the patıents as representatıve of dılu tıonal hyponatremıa

Cardıac output (C O) expressed as cardıac ın dex (C I) was measured ın connectıon wıth rıght heart catheterızatıon accordıng to Fıck s method or by dye dılutıon curves obtaıned after ınjectıon of Cardıo Green (ındocyanıd green) Rıght renal veın catheterızatıon was performed ın all cases Satısfactory posıtıonıng of the catheter tıp ın the renal veın was verıfied by ınjectıon of a small amount of radıographıc contrast materıal and by oxımetry of renal veın and ınferıor vena cava blood samples demonstratıng hıgh oxygen saturatıon ın the former Systemıc arterıal blood samples were obtaıned from an ındwellıng poly ethylene catheter placed percutaneously ın the femoral artery Urıne specımens were obtaıned from an ındwellıng urethral catheter The blad der was emptıed by suprapubıc pressure and rınsed wıth salıne solutıon after each collectıng perıod

The clearance of ınulın (C_{IN}) and para amınohıppurate (C_{PAH}) were studıed usıng a con

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Table I Clinical and laboratory data

Patient no	Age (yr)	Serum Na (mEq/L)	Serum K (mEq/L)	Serum Cl (mEq/L)	Serum standard bicarbonate (mEq/L)	Exchangeable sodium	
						mEq	% of predicted value
1	52	125	5 2	89	23	3 250	150
2	52	130	3 5	89	–	2 610	120
3	62	125	3 6	90	30	2 890	195
4	62	136	4 4	98	22	4 930	130
5	44	131	3 0	95	–	3 840	140
6	54	136	4 3	96	27	3 396	115
7	68	133	3 8	89	–	3 540	100
8	42	130	4 0	95	22	3 950	160
Normal range		137 148	3 5 5 0	98 106	22 26		80 120

stant infusion technique according to the method previously described by Brodwall and Laake[5] Glomerular filtration rate (GFR) was measured as the clearance of inulin Renal plasma flow (RPF) was calculated from C_{PAH} and renal extraction ratio of PAH (E_{PAH}) Renal blood flow (RBF) was calculated from RPF and hematocrit

Serum sodium potassium and chloride concentrations were measured with an AutoAnalyzer and standard bicarbonate with double equilibration Astrup technique Sodium concentration in urine was determined by flame photometry Total exchangeable sodium ($Na_{(e)}$) was measured with the use of ^{24}Na according to the method described by Bauer[6] The results were compared with predicted normal values based on age weight and sex The values obtained for $Na_{(e)}$ were either expressed in mEq or as percentages of predicted normal values for each individual In this study as in other similar studies no correction formulas are used for the weight increase caused by edema The predicted normal values therefore will tend to be too high while values expressed as percentages of normal values will tend to be underestimated[7]

Renal oxygen consumption was calculated from the values of renal blood flow and renal arteriovenous oxygen difference The amount of tubular reabsorption of sodium was calculated as the difference between the amount of sodium filtered and the amount of sodium excreted

All individuals were examined in 1 to 2 periods of 25 to 35 minutes duration The renal function data are corrected to a surface area of 1 73 M^2

Regression lines were drawn according to equations found by the method of least squares. Coefficients of correlation were calculated as described by Snedecor[8] P values higher than 0 05 were not considered to be significant

Results

Comparison between systemic and renal hemodynamics Table II summarizes the results of the simultaneous determination of cardiac and renal function Cardiac output was depressed in all patients in some markedly, indicating a severe degree of heart failure Glomerular filtration rate was on an average 65 ml per minute and renal blood flow on an average was 340 ml per minute Thus in our patients the filtration rate was reduced on an average to approximately 2/3 and the renal blood flow to approximately 1/3 of normal Consequently, the true filtration fraction when determined as the ratio of filtration rate and renal plasma flow (C_{IN}/RPF) was elevated in most cases with an average of 0 35 versus normal mean value approximating 0 20 Even higher values were obtained when the ratio of inulin and PAH clearances was considered

The extraction of para aminohippurate by the kidneys showed large individual variations In 4 out of 8 patients studied extraction of PAH was decreased below lower normal range (82 per cent) As renal blood flow was calculated from

the clearance of PAH corrected for extraction ratio of PAH together with hematocrit the variations in E_{PAH} also explain the disparities between C_{PAH} and renal blood flow

The relationship between systemic hemo dynamics and renal function are plotted in Fig 1 The renal A V oxygen differences which in all cases were higher than normal were inversely related to the cardiac output The diminution of the fraction of cardiac output perfusing the kid neys was independent of the fall in cardiac out put The individual values for filtration fraction did not correlate with the impaired cardiac out put

Exchangeable sodium and renal function studies Relationship between renal hemo dynamic and total exchangeable sodium are shown in Fig 2 There was no significant correla tion between the magnitude of total body sodium content and the glomerular filtration rate or renal blood flow Fig 3 shows that there ap parently existed no significant relationship be tween an increase in total body sodium and ris ing values for the true filtration fraction (C_{IN}/RPF) while the relationship between the former parameter and rising values for C_{IN}/C_{PAH} ratio was significant

Comparison between renal oxygen consump tion and sodium reabsorption The data pertain ing the renal sodium reabsorption and renal ox ygen consumption are given in Table III Despite the variations in absolute quantities of sodium filtered, reabsorbed and excreted in the pa tients a relatively constant fraction of the sodium was absorbed. With two exceptions (Cases 2 and 6) this amounted to more than 99 0 per cent of the quantity filtered which is close to normal The profound alterations in renal glomerular filtration rate were accompanied by corresponding changes in sodium reabsorption which is shown by the fact that the amounts of sodium reabsorbed per 100 ml glomerular fil trate were approximately the same in all pa tients

The renal oxygen consumption apparently varied independently of the amounts of sodium reabsorbed The Na /O_2 ratio for each patient showed large variations A significant direct cor relation existed between values for Na /O_2 ratio and glomerular filtration rate which also was true when Na /O_2 ratio was compared to filtra tion fraction This is shown in Fig 4

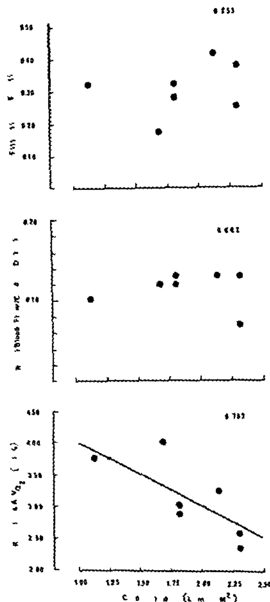


Fig 1 Correlation plot of cardiac index to *Filtration Fraction* (F F) above renal fraction (*Renal Blood Flow/Cardiac Out put*) middle and Renal arterio venous oxygen difference ($R_{A\ V_{O_2}}$) below

Discussion

From a hemodynamic viewpoint all patients included in the present study were characterized by low output failure their cardiac output being reduced to a level at or below one half of the nor mal

The renal blood flow was reduced to a larger extent than the cardiac output comprising on an average approximately 10 per cent of the car diac output This observation is in accordance with the well established homeostatic mecha

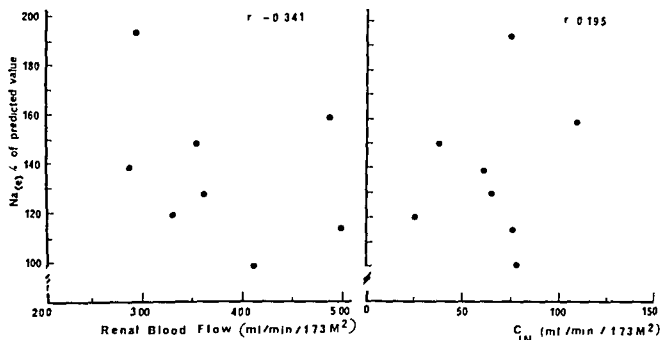


Fig 2 Correlation plot of total exchangeable sodium ($Na_{(e)}$) and Renal Blood Flow (RBF) left or to Glomerular Filtration Rate (C_{IN}) right

Table II Systemic and renal hemodynamics in 8 patients with congestive heart failure (dilution syndrome)

Patient no	CI (L/min/M²)	C_{IN}	C_{PAH}	RPF	RBF	RBF/CO (%)	C_{IN}/RPF (FF)	C_{IN}/C_{PAH}	E_{PAH} (%)	Renal ΔA Vo (vol %)
		mL/min/1 73 M²								
1	1 7	37	113	217	362	0 12	0 17	0 33	52	4 07
2	—	25	108	209	331	—	0 12	0 23	52	6 62
3	2 3	71	119	187	304	0 07	0 38	0 60	84	2 40
4	1 8	65	180	223	360	0 12	0 29	0 36	81	2 94
5	1 1	60	159	190	296	0 10	0 32	0 38	84	3 76
6	2 3	74	230	277	504	0 13	0 26	0 32	83	2 55
7	1 8	77	222	239	412	0 13	0 32	0 35	93	2 95
8	2 1	111	183	269	480	0 13	0 41	0 60	68	3 20

Abbreviations CI = cardiac index C_{IN} = inulin clearance C_{PAH} = para aminohippurate clearance RPF = renal blood flow CO = cardiac output E_{PAH} = para aminohippurate extraction ratio ΔA Vo_2 = arteriovenous oxygen difference FF = filtration fraction

nism of diverting blood from the kidney when the cardiac output is falling although the individual values for renal blood flow expressed as per cent of cardiac output did not correlate with the severity of the impairment of cardiac index This observation is in accordance with other similar studies in this field [9]

Under this circumstance, a significant inverse correlation was found when the cardiac output was compared to the renal arteriovenous oxygen difference, showing that the kidneys respond to a failing cardiac output in a manner similar to muscle and other tissues [10]

In spite of the large decrease in renal blood flow, glomerular filtration rate was reduced to a much lesser extent resulting in an increased filtration fraction which is in accordance with the literature described previously

We were not able to demonstrate any significant relationship when the glomerular filtration rate or renal blood flow were correlated to the amounts of total exchangeable sodium From the

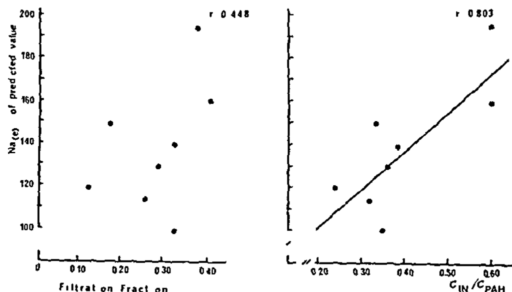


Fig 3. Correlation plot between total exchangeable sodium (Na_e) and *Filtration Fraction* (Glomerular Filtration Rate (C_{IN}/Renal Plasma Flow (RPF)) left or Glomerular Filtration Rate/Para aminohippurate Clearance (C_{IN}/C_{PAH}) right

Table III Urine flow and renal sodium reabsorption and oxygen consumption

Patient no	Urine flow (mL/min.)	Sodium			Reabsorbed Na per 100 mL filtrate (mEq)	Renal oxygen consumption (μMol/min./1 73 M²)	Na^+/O (mEq/μMol)
		Filtered	Excreted	Reabsorbed			
		mEq/min/1 73 M²					
1	0 42	4 657	0 020	4 637	12 53	0 65	7 13
2	0 68	3 260	0 042	3 218	12 87	1 84	1 75
3	1 09	8 913	0 033	8 880	12 51	0 30	29 60
4	1 00	8 722	0 044	8 678	13 35	0 47	18 46
5	0 72	7 923	0 025	7 878	13 16	0 49	16 12
6	10 60	10 342	0 838	9 504	12 84	0 57	16 67
7	1 25	10 288	0 021	10 267	13 33	0 54	19 01
8	1 36	14 453	0 038	14 415	12 99	0 69	20 89

literature it is evident that the influence of the two former parameters on sodium reabsorption and excretion in cardiac failure is indeed obscure A low glomerular filtration rate is a common finding in many patients with congestive heart failure but in some cases the kidneys retain sodium in the presence of normal filtration rate [11,12] Clinical decompensation may occur in cardiac patients without significant changes in filtration rate [13] A reduction in renal blood flow is associated with a reduction in urinary sodium excretion However the decrease in renal blood flow with a smaller decrease in filtration rate might lead to simultaneous alterations in either peritubular hydrostatic pressure or protein concentrations or both, which may result in no net effect on absolute sodium excretion as stated by Vander and associates [14]

It is of particular interest that the present study did not demonstrate any significant correlation between the magnitude of the exchangeable sodium on the one hand and filtration

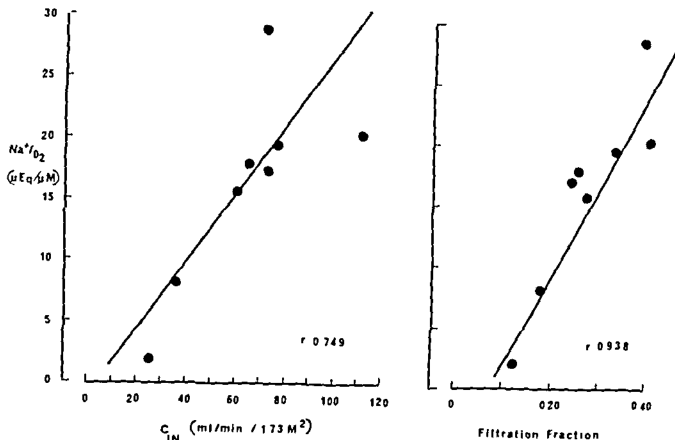


Fig 4 Correlation between Net Sodium Reabsorption per mole of Oxygen Consumed (Na^+/O_2) and Glomerular Filtration Rate (C_{IN}) left or *Filtration Fraction* to right

fraction on the other However the correlation became significant when the former parameter was plotted against the ratio of glomerular filtration rate to C_{PAH} This discrepancy is due to the fact that in our study extraction of PAH was decreased in several patients thus distorting the expected linear relationship between renal blood flow and C_{PAH} The observation that the extraction of PAH declines in patients with congestive heart failure is in accordance with studies by Gomori and colleagues [15] Porter and co workers[9] also found low values for E_{PAH} in some of their patients *

There is strong evidence against the high filtration fraction hypothesis Although high values for filtration fraction has been reported in cardiac patients it is apparent that this may be found in edematous as well as in non edematous states [16] A high filtration fraction has furthermore been found in patients with hyper tensive heart disease and in patients with cor pulmonale but not in cardiac failure [17] Consequently the present study as well as many other actual studies support the view that a high filtration fraction is not the determining factor for the sodium and water retention seen in cardiac failure

In the present study no correlation existed between the values for filtration fraction and the cardiac output In this way our findings seem to differ from other studies where an inverse relationship has been described when filtration fraction values were plotted against cardiac output [9] The latter study was, however, made on patients with generally higher cardiac output values than ours

It is well recognized that the main part of the renal oxygen consumption is utilized in the active reabsorption of sodium [18 20] with a close correlation between oxygen consumption and active sodium transport. The lack of correlation between these two parameters found in our study should therefore be commented upon more closely Previously some clinical studies have been published where a disparity between the sodium reabsorption and the oxygen consumed in the kidneys was found [6] More recently experi

* In the present study however the low extraction of PAH in patients No 1 and 2 (Table II) might be due to an over all reduction in renal function as will be seen from a depressed glomerular filtration rate and renal blood flow In patient No 8 glomerular filtration rate was in the normal range

mental studies in animals after different diuretic drugs also support the possibility of a passive tubular sodium transport or reabsorption not involving active aerobic sodium transport mechanisms [21,22] Our data is in accordance with Porter and colleagues [9] who found great variations in the Na^+/O_2 ratio in a group of heart patients Thus in heart failure oxidative processes apparently seem to be to a smaller degree involved in tubular sodium reabsorption than under normal conditions

In contrast to us however the authors referred to above also found an inverse correlation between Na^+/O_2 ratio and filtration fraction although they apparently had difficulties in explaining the finding In our study the demonstration of a significant positive correlation between Na^+/O_2 ratio and filtration fraction favors the assumption that in the more advanced degree of congestive heart failure at least some part of the sodium may passively be reabsorbed

Recently in dogs with experimental heart failure a shift in blood flow from renal cortex to outer medulla was found in regional flow studies using an inert radioactive gas technique [23] This mechanism means involvement of perfusion of nephrons with longer loops of Henle and with greater capacity for passive sodium reabsorption and may be of theoretical interest when discussing our patients

Summary

In the present series cardiac output renal blood flow corrected for PAH extraction rate and glomerular filtration rate were measured in 8 patients with decompensated congestive heart failure with hyponatremia and normal or increased exchangeable sodium (dilution syndrome) The renal sodium reabsorption and oxygen consumption have also been measured

The cardiac output was reduced to less than half the normal The renal blood flow was reduced to a greater degree than cardiac output indicating a specific diversion of blood away from the kidneys The glomerular filtration rate was also reduced, but to a lesser extent than the renal plasma flow giving filtration fractions higher than usually reported. The reduction in renal blood flow and in glomerular filtration rate or the increase in filtration fraction had no relation to the magnitude of exchangeable sodium

In our patients, variations in the glomerular filtration rate revealed constancy in the sodium reabsorptive mechanism The renal oxygen consumption was found to vary independently of the sodium reabsorption The findings were compatible with an increased passive back diffusion of sodium in the tubular lumen in patients with advanced congestive heart failure Data from the present study support the assumption that such passive re entry for sodium is related to an increased filtration fraction although other mechanisms must also be considered.

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U wave alternans An electrocardiographic sign of left ventricular failure

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The U wave of the electrocardiogram was recognized and named by Einthoven in 1912 For sixty years despite efforts to explain it its cause and significance remain a mystery [1]

U waves in many clinical situations were observed over the past twelve years One constantly recurring pattern seen in normals was a larger U wave in the first beat after any pause a phenomenon described by Scherf and Bornemann [2] In 1971 postextrasystolic U wave alternans was seen for the first time in an elderly man hospitalized for acute left ventricular failure This U wave pattern was easily identified for several reasons—the rate was not excessive the tracing was unmounted, and the leads were long U waves were clearly present and premature ventricular contractions were frequent Before postextrasystolic pulsus and U wave alternans could be recorded he responded to therapy Since then ten patients with compensated left ventricular failure have had postextrasystolic pulsus and U wave alternans documented on an Electronics for Medicine recording in the catheterization laboratory In each case the characteristics were the same and in no other situation was U wave alternans encountered

Examples

Fig 1 shows the left ventricular pressure and a mid chest lead following a premature ventricular contraction in a normal patient. Despite the higher systolic pressure after a pause noted peripherally the left ventricular systolic pressure is actually lower than in subsequent beats an observation recently described by Beck and colleagues [3] The longer the pause the larger the stroke volume and the bigger the U wave

Table I lists the patients showing postextrasystolic pulsus and U wave alternans The transverse cardiac diameter measured in millimeters on a standard six foot chest x ray is compared with the predicted value for height and weight Four patients showed subtle constant alternans All had the brachial or left ventricular pressure and chest lead showing U waves recorded following a spontaneous or induced premature ventricular contraction

Fig 2*A* shows patient No five There is very subtle constant pulsus and U wave alternans Figs 2*B* and *C* show the response after one and two premature ventricular contractions The U waves are numbered for clarity Transient exaggeration of both pulsus and U wave alternans is clearly apparent

Fig 3 patient No nine showed transient pulsus alternans for a few beats after each pause U waves one and three are greater than waves two and four as they gradually become uniform

Fig 4 patient No two showed U wave alternans after a pause as well as a suspicion of T wave alternans as described by Warbasse and Dodge[5] (see Discussion)

Fig 5 patient No ten with hypertension and a patent ductus shows an elevated left ventricular end diastolic pressure Fig 5*A* shows a mild pause followed by a single larger beat and larger U wave without pulsus or U wave alternans Fig 5*B* shows the same patient after a longer pause transient left ventricular alternans is seen and the arrows indicate the U wave alternans seen in V_3

One second time lines are present on some ex

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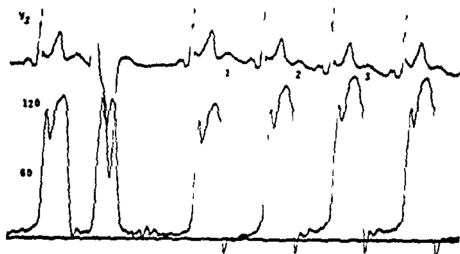


Fig 1 Normal postextrasystolic left ventricular pressure and U wave response

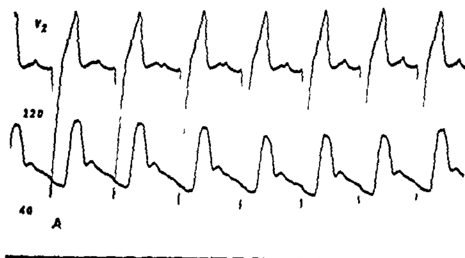


Fig 2A Subtle brachial artery and U wave alternans before a premature ventricular contraction

Table I Patients observed to have postextrasystolic pulsus and U wave alterans

Patient no and initials		*Age*	*Sex*	*Diagnosis*	*Heart size* patient/ normal*	*Gallop*	*Pulsus alternans*
1	R R	69	M	Coronary disease	165/129	Ventricular	Post PVC
2	W B	71	M	Aortic stenosis (post op)	210/144	Ventricular	Constant
3	W M	61	M	Hypertension	165/139	Atrial	Constant
4	A M	66	M	Alcoholic cardiomyopathy	170/144	None	Post PVC
5	R A	52	M	Non coronary cardiomyopathy	200/120	Ventricular	Constant
6	R M	63	M	Coronary disease	190/118	Ventricular	Constant
7	C J	63	M	Coronary disease	170/129	Atrial	Post PVC
8	D S	80	M	Hypertension	160/130	None	Post PVC
9	D C	62	F	Non coronary cardiomyopathy	170/123	Ventricular	Post PVC
10	R A	59	M	Patent ductus and hypertension	180/143	None	Post PVC

*Heart sizes are in millimeters vs predicted normals

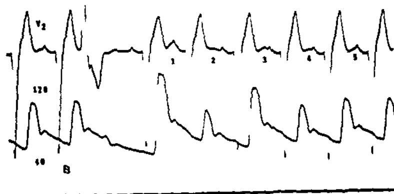


Fig 2B Following a premature ventricular contraction (PVC) the pulsus and U wave alternans are accentuated

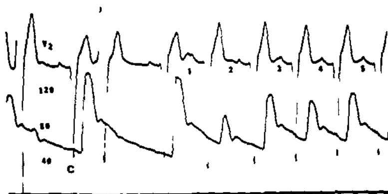


Fig 2C The same patient depicted in Figs 2A and B after bigeminy

amples The paper speed was the same on all Some variability in stroke volume resulting from respiration and in some instances by slight changes in R R intervals undoubtedly occurred. It should be emphasized, however that the postextrasystolic events were recorded repeatedly in each patient and on each occasion the transient U wave and pulsus alternans were the same

Discussion

Although this is the first report of pulsus and U wave alternans indicating left ventricular failure a search of the literature revealed a previous example Discussing alternations of the heart Littmann[4] showed an example of postextrasystolic pulsus alternans illustrating left ventricular failure The accompanying electrocardiographic lead showed U wave alternans but this went unrecognized

Mullican and Fisch[5] reported a 39 year old alcoholic with huge U waves showing striking postextrasystolic alternans subsiding within a few days If the concept that U wave alternans indicates an alternating stroke volume is confirmed one could postulate that thiamine deficient patients with left ventricular failure could show U wave alternans Larger than normal U waves suggesting large vigorous stroke volumes would also be anticipated

Warbasse and Dodge[6] published an abstract relating postextrasystolic pulsus and T wave alternans. Two of their examples were examined. They emphasized that if the second T wave following a premature ventricular contraction was different pulsus alternans was also present Figs 4 and 5B may be illustrations of this

Seeking a theory of U wave production consistent with clinical observations through the years led to the conviction that it reflects a mechanical rather than an electrical event The timing of the U wave corresponds to left ventricular relax

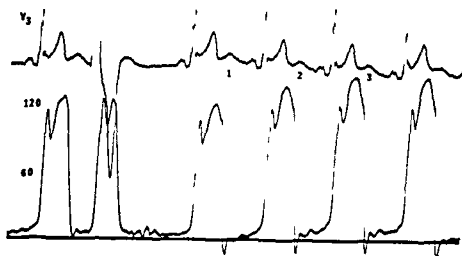


Fig 1 Normal postextrasystolic left ventricular pressure and U wave response

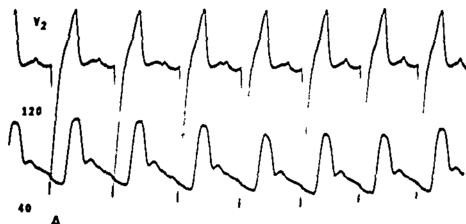


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Heart sizes are in millimeters vs predicted normals

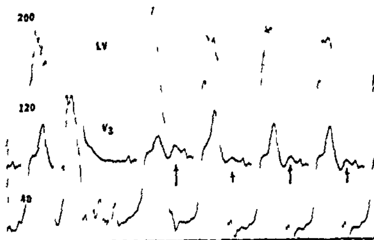


Fig 58 Patient No 10 following a longer pause shows transient pulsus and U wave alternans *Arrows* indicate the U waves.

ation and the size of the U wave corresponds to the vigor of the recoil Whether it represents movement accentuation of an electrical vector or more likely merely a movement artefact it provides a valuable electrocardiographic clue of left ventricular action Suspecting that the end systolic volume alternates in postextrasystolic pulsus alternans resulting in variable vigor of recoil postextrasystolic U wave alternans was anticipated and watched for Encouraging technicians to watch for premature ventricular contractions while taking midchest leads and to include the next few beats when trimming and mounting the tracing should enhance the recognition of this electrocardiographic sign of heart failure

Summary

All postextrasystolic complexes seen over a twelve year period were carefully analyzed Normally only the first complex is different, showing a slightly altered T and a larger U wave Ten patients with left ventricular failure and postextrasystolic pulsus alternans consistently showed postextrasystolic U wave alternans Besides introducing an electrocardiographic sign of heart failure this provides some insight into the underlying etiology of the U wave

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Fig 3 Postextrasystolic pulsus and U wave alternans in a patient showing no alternans prior to the premature ventricular contraction



Fig 4 Accentuation of U waves 1 3 and 5 in a patient with left ventricular failure



Fig 5A Patient No 10 showing an accentuated left ventricular pressure and larger U waves after a slight pause *Arrows* indicate the U waves

progressive decline in the R wave height from V_1 or V_2 to V_4

VCG—Anterior Infarction Initial few milli seconds anterior but by 20 msec or earlier the vector in both the right sagittal and transverse plane is newly posterior to the F point Inscription of the initial vector in the right sagittal plane which is shifted from clockwise to counterclockwise strongly suggests extension to the apical or inferior wall [8,10] Although these patients might therefore be listed as double surface infarction we chose to utilize this as only a supporting criterion for anterior infarction unless there were other criteria for inferior infarction

ECG—Lateral or Anterolateral Infarction (1) New Q wave 04 sec or greater in Leads I aV_L V_5 and V_6

VCG—Lateral or Anterolateral Infarction (1) A shift in the frontal plane initial inscription from clockwise and leftward to counterclockwise and rightward for at least 25 msec (2) A shift in the initial transverse plane vector from anterior rightward counterclockwise to anterior leftward clockwise The mid and terminal loop may remain clockwise or become counterclockwise in a figure of 8

Since many of the patients entered surgery with old myocardial infarctions only new changes were utilized as evidence for perioperative damage ECG changes which met criteria on only one of the two postoperative cardiograms were not included as infarction After independent readings were recorded the results of ECG and VCG readings were compared The differences in voltages (Tables II and III) were evaluated by a two tailed test of differences between means of paired data[11] and by a two way analysis of variance of differences between groups and times of ECG s [12] The differences in frequency of events between groups (Table IV) were evaluated by Fisher s exact test [13]

Results

Table I shows the frequency with which various infarctions were diagnosed. Perioperative myocardial infarctions occurred very frequently in this group of patients ranging from 40 to 46 per cent by either of the techniques Only two of 35 (6 per cent) of the ECG classifications differed from the VCG A total of five new inferior infarctions were diagnosed including those in association with other new infarctions and there were no quantitative or qualitative differences in diagnoses between the ECG and VCG The number of cases thought to have some form of anterior infarction by each mode was similar but two patients who clearly had VCG criteria for anterior or anteroseptal infarction were not diagnosed by plain ECG Lateral or anterolateral infarction changes were not seen in pure form Two patients did have ECG and VCG criteria for anterior infarction with an initial counterclockwise transverse plane inscription. Three patients had striking new Q waves in both the anterior precordial and inferior leads with typical VCG changes which were diagnosed as both anterior and inferior infarction

A change in the direction of inscription in the right sagittal plane initial vector from clockwise to counterclockwise is a vector criterion in anterior infarction[8,10] which cannot be appreciated from the ECG (Fig 1) This criterion strongly suggesting extension of the anterior infarction to the apical or inferior wall was seen in 11 of the 13 patients with the initial 20 msec vector posterior Two additional patients had this change alone which was not considered adequate by itself to diagnose anterior or inferior infarction

Non specific changes Although ECG and VCG changes in ST segment height shape and vector as well as T wave polarity symmetry and rotation are helpful in non surgical infarction they occurred in this study without any recog

Table I Diagnosis of types of perioperative infarction by ECG and VCG

	Diagnosis by ECG		*Diagnosis by VCG*	
	No	*(%)*	*No*	*(%)*
No changes of infarction	21	60	19	54
Inferior infarction	3	9	3	9
Anteroseptal infarction	5	14	5	14
Anterior or anterolateral infarction	4	11	6	17
Double surface infarction	2	6	2	6
Total	35	100	35	100

Anterio and inferior inf rction.

The incidence and clinical significance of ECG-VCG changes of myocardial infarction following aortocoronary saphenous vein bypass surgery

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Prevention of myocardial infarction is one of several goals of aortocoronary saphenous vein jump graft surgery Yet the reported incidence of myocardial infarction or 'damage varies widely from 4 to 58 per cent[1-7] The cause and meaning of electrocardiographic changes following surgery are often unclear The purpose of the following study is twofold (1) to examine the relative frequency of perioperative electrocardiographic (ECG) and vectorcardiographic (VCG) changes of myocardial infarction and (2) to compare the clinical course of patients with VCG diagnosed infarction with the course of patients without significant change

Methods

The patient population is made up of 35 consecutive patients undergoing elective jump graft surgery for angina pectoris Patients were excluded from the study for any of the following reasons (1) myocardial infarction in progress at the time of surgery (2) symptoms of severe congestive heart failure before surgery, (3) aneurysmectomy at the time of surgery and (4) death before follow up VCG or ECG could be obtained

Standardized 12 lead ECG s were collected immediately before, within 96 hours after and within 10 weeks after surgery These were placed in sequence and numbered 1, 2 and 3 respectively The vectorcardiograms were collected using the Frank leads and were recorded on Polaroid film using a Hewlett Packard Model 1507A vector programmer Dots were recorded every 2 5 msec in frontal right sagittal and transverse planes in both low sensitivity and blown up views for examination of the initial and T vectors VCG s were usually collected immediately before and within 10 weeks after surgery at the same time as the No 1 and 3 ECG The ECG s and VCG's were marked before and after and were read and discussed in sequence by at least two of the authors without knowledge of the patient's name, clinical outcome or the other ECG or VCG results utilizing criteria given below Perioperative cardiac enzymes were not systematically gathered

ECG VCG criteria for recent infarction

ECG—Inferior Infarction New Q waves 04 second or greater in III a V_F with Q in II 02 second or greater

VCG—Inferior Infarction Initial QRS vectors on both the frontal and right sagittal plane which is newly superior to the E point for at least 35 msec

ECG—Anteroseptal Infarction New Q QS or QR in V_1 and V_2 with a Q at least 04 sec duration

VCG—Anteroseptal Infarction Initial QRS vector on both the transverse and sagittal plane newly moves directly posterior to the E point

ECG—Anterior Infarction (1) Small or large R in V_1 with a Q or QS at least 04 sec duration in the mid precordial leads or (2) R in V_1 with

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Table IV Follow up clinical course of surviving patients according to presence or absence of perioperative VCG changes of infarction*

	Patients with no perioperative infarction		Patients with peri operative myocardial infarction		Fisher s exact test (13)
	No	(%)	No	(%)	P
Improve 2 or more NYHA Classes	8	42	6	46	0 70
Improve 0 1 NYHA Classes	10	53	6	46	0 50
Worse 1 or more NYHA Classes	1	5	1	8	0 65
NYHA Class 1 patients postoperative	9	48	6	46	0 62
New symptoms of congestive heart failure	2	11	4	31	0 16
New papillary muscle murmur	0	0	4	31	0 02
Congestive heart failure and/or new papillary muscle	2	11	7	54	0 01
Persistence of angina pectoris	5	26	7	54	0 11
Additional myocardial infarctions 10 weeks or later after surgery	1	5	5	38	0 03
Total	19	100	13†	100	

*Average follow up 1 year

†Three deaths not included.

regularly accompanied by voltage loss in both ECG and VCG with or without infarction immediately after or weeks after surgery Table II shows the loss of R wave height with surgery seen in Leads V_4 and V_5—the leads most commonly used to diagnose anterior infarction when R wave height criteria are used. In both Leads V_4 and V_5 there is a significant loss of R wave amplitude both immediately after and weeks after surgery Similar loss of R wave was seen in V_6 and in several frontal plane leads In V_4 this loss was significantly greater in the anterior infarction group than in the non infarction group (P less than 02) while in V_5 and V_6 it was not In an attempt to develop reliable R wave height or loss of height criteria which would specifically separate the patients with VCG anterior infarction from those without we tried the following R wave less than 5 mm in V_1 through V_4 R in V_5 less than 8 mm [14] loss of height of V_4 or V_5 R wave equal to or greater than two standard deviations of the mean loss of R wave in the non infarction group greater than 50 per cent loss of R wave voltage in V_4 or V_5 a screening curve for false positives and negatives in V_4 [15] Although the majority of patients with VCG anterior infarction were included utilizing any of these criteria or techniques, there were always several patients included who had no VCG evidence of anterior infarction Thus we were unable to consistently separate patients with VCG anterior infarction from those without such changes by change in R wave height alone without an excessively high false positive or false negative rate

Examination of vector loops as well commonly showed a symmetric shrinking of the loop with little if any change in the initial middle or terminal shape or rotation (Fig 2) Table III demonstrates the changes in maximal VCG, QRS loop voltage after surgery Significant loss of maximal voltage is seen in frontal and transverse planes Loss of voltage seen in patients with VCG anterior infarction was not statistically different from those without infarction Thus a newly posterior 20 msec vector in these patients was not a result of a non specific voltage loss or loop shrinkage

Clinical outcome of VCG changes All three of the late deaths occurred in patients with VCG changes of perioperative infarction One patient with a double jump graft who had a perioperative anterior infarction with congestive heart failure died suddenly six weeks postoperatively At postmortem both grafts were occluded with organized thrombus There was extensive an

Table II Changes in R wave height in Leads V_4 and V_5 immediately after (ECG 1 – ECG 2) and weeks after (ECG 1 – ECG 3) surgery according to whether ECG indicated anterior infarction

Lead	Group	ECG 1 minus ECG 2					ECG 1 minus ECG 3				
		ECG 1 mean (mm.*)	ECG 2 mean (mm.)	Difference of means (mm.)	Std deviation difference (mm.)	P	ECG 1 mean (mm.)	ECG 3 mean (mm.)	Difference in means (mm.)	Std. deviation difference (mm.)	P
V_4	Patients with no anterior infarction	12 3	8 2	-4 1	1 1	<001	12 3	9 0	-3 3	0 9	<001
	Patients with new anterior infarction†	11 8	2 9	-8 9	1 9	<001	11 8	2 4	-9 4	1 9	<001
V_5	Patients with no anterior infarction	13 0	9 3	-3 7	0 8	<001	13 0	10 9	-2 1	0 5	<001
	Patients with new anterior infarction	14 4	6 7	-7 7	1 7	<001	14 4	6 9	-7 5	1 6	<001

Height of R wave measured in millimeters. All ECG s standardized such that 1 millivolt = 10 millimeters
†Postoperative VCG has 20 msec vector newly posterior in transverse and right sagittal plane

Table III Change in maximal vector voltage in each plane after surgery according to whether VCG shows new anterior infarction

Group	Plane	Mean maximal voltage before surgery*	Mean maximal voltage after surgery	Difference of means	Stand deviation difference in means	P
Patients with no anterior infarction	Frontal	1 37	0 99	-0 38	08	<001
	Transverse	1 40	1 23	-0 17	03	<001
	Right sagittal	1 01	1 00	-0 01	05	NS
Patients with new anterior infarction†	Frontal	1 61	1 06	-0 55	007	<001
	Transverse	1 62	1 25	-0 37	08	<001
	Right sagittal	0 98	1 07	+0 09	04	NS

Maximal voltage of QRS vector in millivolts
†Postoperative VCG has 20 msec vector newly posterior in transverse and sagittal plane

nizable relationship to QRS abnormalities of infarction The regular use of varying amounts of digitalis as well as the frequency of postoperative *pericarditis rendered* such changes non specific

In comparing our readings of these ECG s with those officially rendered and returned to the patients chart we discovered considerable variation and confusion as to how to read poor R wave progression in the anterior precordial leads In four patients with no other ECG or VCG changes except a decrease in the anterior R waves, the patients were diagnosed on the official readings as anterior infarction Several others with comparable losses of R wave were called non specific changes changes due to lead placement or changes due to surgery

It was then apparent that surgery was

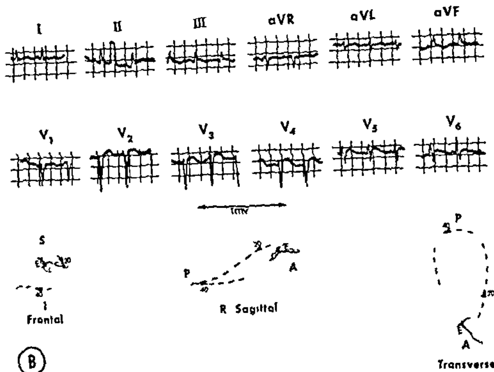


Fig 1B For legend see opposite page

frequently had myocardial damage than patients without VCG changes (2/9 p = 01)

Persistence of angina requiring nitroglycerin was common in both groups despite a decrease in the clinical severity of angina Although more patients had persistence of angina in the infarction group the difference did not reach statistical significance (P = 0 11) Persistence of angina predicted further new infarction within the first year significantly more often (P = 0 03) in the perioperative infarction patients (5/7) than in those without infarction (1/5)

Discussion

Other than one autopsy we have no conclusive proof in this study as to which patients actually did suffer infarctions Comparison of the sensitivity and specificity of the ECG and VCG in predicting infarction has been reported in many previous studies Simonson and co workers[16] in in a review of the literature prior to 1965 found that VCG s were considered superior to the ECG s in the majority of the papers reviewed The diagnostic accuracy of both ECG and VCG was greatest in acute and anterior infarction In this same study in anterior infarction the VCG (81 per cent) was superior to the ECG (67 per cent) while no clear superiority was seen for other infarctions Indeed, in our study there was no difference between ECG and VCG in the inferior or double surface infarction category In the diagnosis of anterior infarction where there were variations between the two modes the VCG should prove to be the most useful and valid.

While many criteria for infarction have been proposed we have selected measurable ECG criteria which would almost universally be accepted as diagnostic of infarction VCG criteria are not as well established. While it is tempting to read changes in the loop shape or in the middle and late portion of the loop as evidence of infarction[8-10] such changes are often subjective and difficult to quantitate It is generally agreed that changes in the position and direction of inscription of initial vectors constitute the most reliable criteria for infarction Most authors require between 25 and 30 msec superior to the E point for the diagnosis of inferior infarction The five patients in this study with diagnosis of inferior infarction all had superior forces in two planes of 35 or more msec

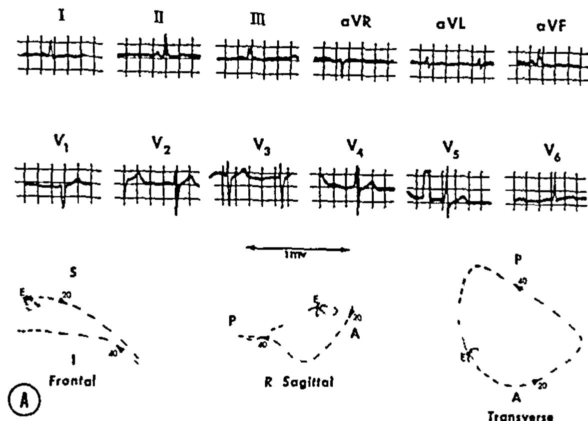


Fig 1 A and B *A* Preoperative (Nov 29 1971) ECG and VCG *B* Postoperative (Feb 4 1972) ECG and VCG Typical new VCG changes of anterior infarction postoperatively Note the change in right sagittal plane inscription from clockwise preoperatively to counterclockwise postoperatively along with posterior shift of the 20 msec vector This patient had no pathologic Q waves Arrows indicate direction of loop inscription and numbers indicate the position of the loop at 20 and 40 msec

terior wall fibrosis, expecially in the area distal to the left anterior descending anastomosis which was consistent with the ECG and VCG diagnosis Two other patients with anteroseptal infarction at the time of surgery recovered and were improved I and II New York Heart Association (N Y H A) classes respectively One patient had occasional premature ventricular contractions but no angina while the other had angina only on exercise testing (450 km) Both of these patients died suddenly and unexpectedly seven and eight months postoperatively No autopsy on these patients was obtained

Table IV shows the clinical outcome of the 13 infarction patients surviving to date and the 19 patients without infarction divided on the basis of VCG criteria Patients were followed on the average of 12 months and were seen on the average of 3 times postoperatively Clinical classification by the New York Heart Association criteria revealed no significant differences between the two groups Four patients in the infarction group and two patients in the group without significant changes in the VCG developed new symptoms of congestive heart failure requiring the institution of digitalis and diuretics The frequency of congestive heart failure was not high enough to demonstrate a significant difference between the two groups (P = 0 16) Although these six patients initially, after surgery, had a higher (poorer) N Y H A classification the institution of digitalis resulted in marked improvement in three of four of those with and in one of two of those without perioperative infarction These patients then, were finally classified in a lower (better) N Y H A classification than either their initial post operative or the preoperative N Y H A classification In the infarction group three additional patients developed new, persistent apical late systolic murmurs attributed to papillary muscle dysfunction without symptoms of congestive heart failure Taking new papillary muscle damage or new congestive heart failure as clinical criteria for perioperative damage patients with perioperative infarction (7/13) more

same direction initial forces may become superiorly and posteriorly directed enough to mimic anterior and inferior infarction as is sometimes seen in patients with emphysema[21] No studies are yet available which demonstrate a systematic change in the anatomic position of the heart of this degree after cardiovascular surgery

Changes in thoracic impedance may cause ECG and VCG changes by altering electrical field distribution[22] Such impedance changes have been shown to occur in patients with chronic obstructive pulmonary disease where the maximal QRS and T vectors are more posteriorly and inferiorly directed and of smaller magnitude[23] This also could explain the diffuse non specific changes in maximal vector voltage in two planes and the loss of anterior R wave in the ECG in our patients. We are unaware how ever of any studies showing changes in the rotation or placement of the initial vector due to changes in thoracic impedance

Others have commented upon the benign course of patients with perioperative ECG VCG changes of damage[24] Although mortality rate figures may appear to be quite low with perioperative infarction early death before standardized, sequential ECG s or VCG s may selectively remove from consideration those patients who succumb quickly to myocardial damage Under these circumstances late death is a better criterion by which to judge the meaning of perioperative electrocardiographic changes. Thus in this study the only late deaths occurred in patients with VCG changes of perioperative infarction

The failure to demonstrate clearcut functional New York Heart Association Classification differences suggests that the perioperative VCG changes are not helpful in predicting morbidity Difficulties in the utilization of this form of classification for patients with angina pectoris have been pointed out by Selzer and Kohn[25] Thus in several of our patients there appeared to be an exchange between angina pectoris and congestive heart failure with a net ultimate improvement in exercise tolerance The much higher incidence of new symptoms of congestive heart failure and papillary muscle damage in the group with infarction changes however is strong evidence that these changes do predict significant myocardial damage In addition the frequent persistence of angina and the occurrence of later further infarction in the perioperative infarction group suggest that the VCG changes help to predict inadequate surgical correction and graft closure

We conclude that myocardial infarction during jump graft surgery is common and is an important cause of late morbidity and death Utilization of R wave loss alone will result in considerable confusion as to which patients actually had infarctions Careful utilization of the ECG criteria given or the utilization of the vectorcardiogram should significantly increase the quality of diagnoses made and help to predict death graft failure early congestive heart failure and further infarctions Future work to determine positional changes of the heart and thoracic impedance changes with surgery as well as careful clinical follow up studies will help to further clarify criteria for perioperative infarctions

Summary

The electrocardiogram and vectorcardiogram were analyzed in 35 consecutive patients before and after undergoing elective aortocoronary saphenous vein bypass grafting for angina pectoris Typical changes of perioperative myocardial infarction were seen in 40 per cent (ECG) and 46 per cent (VCG) Changes of ST segments and T wave could not be correlated with QRS changes of infarction Surgery with or without infarction resulted in a loss in R wave voltage in anterior and lateral precordial leads (V_4 V_5 and V_6) as well as in a symmetric shrinkage of the vector loop in the transverse and frontal planes

Comparing one year follow up results of those with versus those without perioperative VCG changes of infarction showed that late death clinical evidence of myocardial damage and reinfarction were more frequent in the infarction group However no difference in N Y H A functional classification congestive heart failure alone or persistence of angina pectoris could be demonstrated between the two groups The ECG and VCG changes of perioperative infarction are common with this operation and helped to predict late morbidity and death

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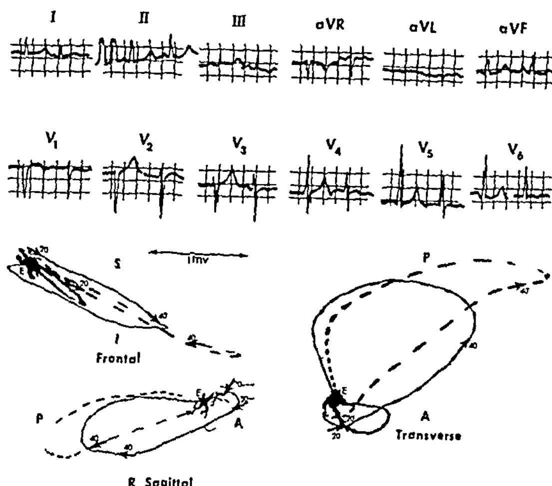


Fig 2 Non specific voltage loss with surgery *At top* the first beat of each lead is from the preoperative ECG (Jan. 17 1972) and the second beat from the postoperative ECG (Feb 17 1972) *Note the decrease in R wave height in* V_4 to V_6 *Bottom*, the postoperative VCG in solid line is superimposed at the same sensitivity on the preoperative VCG in dots *Note the symmetric shrinking of the loop with surgery with no evidence of infarction Arrows* indicate the direction of loop inscription and numbers indicate the position of the loop at 20 and 40 msec

Hugenholtz and colleagues[8] have indicated a high sensitivity for anterior infarction when the 20 msec vector is posterior to the E point This criterion has proven to be highly reliable when left ventricular hypertrophy left bundle branch block, and some forms of cor pulmonale are ruled out [18,20] None of our patients had clinical evidence for cor pulmonale or ECG VCG evidence for left bundle branch block Although three of our patients had ECG and/or VCG voltage and ST segment criteria for left ventricular hypertrophy none actually had a preoperative posterior 20 msec vector Only one of those three had a newly posterior 20 msec vector after surgery Thus left ventricular hypertrophy was not an important factor in producing false positive VCG changes The change in the inscription of the right sagittal plane from clockwise to counterclockwise is a supporting vector criterion for extension of anterior infarction and we therefore did not assign patients with this criterion alone to the infarction group However, this sagittal plane change did occur in 85 per cent of the patients with a new 20 msec posterior vector, lending further support to the diagnosis of infarction in these patients

Multiple factors other than myocardial damage in the operated patients might contribute to ECG and VCG changes Surgery could shift the position of the heart in the chest cavity posteriorly and rotate it around its long axis making the left ventricle more posterior and the vector of the ventricular septum more superiorly oriented Such changes should produce a posterior orientation of the maximal QRS vector and diminish anterior R wave and maximal voltage, as were seen in this study With even further position shift of the heart in the

The electrophysiological effects of intramuscular quinidine on the atrioventricular conducting system in man

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Quinidine is a commonly used drug for the treatment of a variety of cardiac rhythm disturbances [1-10] The effect which this drug has on the electrophysiological properties of the various components of the atrioventricular conducting system has been extensively studied in experimental animal models [11-28] Clinical effects have been primarily evaluated using standard electrocardiographic recordings [29-34] The purpose of this study was to evaluate the effects of intramuscularly administered quinidine gluconate on the electrophysiological properties of the atrioventricular conducting system in man using His bundle electrograms

Methods

Twenty one patients underwent right heart catheterization in the non sedated post absorptive state after informed consent was obtained. The pertinent clinical data of these patients are given in Table I No patient was receiving other antiarrhythmic agents at the time of the study A quadripolar electrode catheter was percutaneously introduced into an antecubital vein and was advanced to the high right atrium near its junction with the superior vena cava The distal pair of electrodes were used to stimulate the atrium and the proximal pair to record a high atrial electrogram A tripolar electrode catheter was introduced through the right femoral vein and was positioned across the tricuspid valve to obtain the His bundle electrogram as previously described [35] Intracardiac electrograms ECG Leads I II III and V_1 and time lines generated at 10 and 100 msec intervals were simultaneously displayed on a multichannel oscilloscope and relayed to a tape recorder Records were later retrieved at a paper speed of 150 mm. per second.

A V nodal and His Purkinje conduction times were measured at sinus rhythm and during atrial pacing QRS duration and QTc interval corrected to a cycle length of 1 000 msec were recorded as a measure of intraventricular conduction and repolarization respectively Spontaneous atrial cycle length was taken as the average of six consecutive sinus beats

Refractory periods of the atrium A V node and His Purkinje system were determined by the extrastimulus method.[36] Electrical stimulation of the heart was performed using a digital stimulator which delivered rectangular impulses of 1 5 msec duration at twice diastolic threshold. The atrium was driven at a basic cycle length (A_1

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Table II Effects of quinidine on spontaneous atrial cycle length A V nodal and His Purkinje conduction and QRS and QTc intervals

Patient	A H (msec)		H V (msec)		CL (msec)		QRS (msec)		QTC (msec)		Mean quinidine Level (mg/L)
	Before	After	Before	After	Before	After	Before	After	Before	After	
1	80	100	40	45	685	700	115	120	400	470	6
2	110	105	60	70	875	790	150	150	410	455	4 2
3	8[illegible]	80	60	65	750	570	140	155	435	465	2
4	8[illegible]	85	40	45	760	720	125	140	434	475	2
5	160	130	50	50	1 000	930	95	100	395	46[illegible]	7
6	70	65	42	50	8[illegible]0	850	90	90	395	41[illegible]	5
7	90	80	[illegible]0	60	935	740	95	95	401	486	6
8	80	90	45	55	715	790	110	120	400	426	4 2
9	100	115	40	50	710	730	100	105	380	443	5
10	80	80	45	50	815	1 020	9[illegible]	95	420	426	4 5
11	140	120	70	80	720	720	160	170	473	508	3
12	100	95	45	50	1 150	950	95	110	422	438	2
13	100	100	48	5[illegible]	870	850	110	110	488	410	3 5
14	80	[illegible]5	60	6[illegible]	800	600	150	150	394	486	7
15	80	80	55	60	775	625	140	145	449	510	4
16	82	82	48	52	760	725	90	90	397	4[illegible]4	6
17	85	60	50	55	830	730	90	90	364	394	7 5
18	80	75	50	60	950	825	85	100	395	455	4 2
19	90	90	50	55	1 450	1 100	95	95	335	396	5
20	130	140	50	50	800	660	100	100	409	449	3 8
21	72	72	50	56	860	830	100	110	338	364	4 5
Mean	94	91	51	[illegible]7	860	783	111	116	402	446	4 6

Relative refractory period (RRP) of the His Purkinje system is defined as longest H_1 H_2 interval at which H conducts to the ventricles with a longer H V time than the basic drive beat or with a QRS of aberrant configuration Although it is recognized that the HPS is a trifascicular system in the absence of multiple recording sites along individual fascicles it is not always possible to distinguish the FRP from the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit

Results

Table II lists the effects of quinidine on spontaneous atrial cycle length A V nodal and His Purkinje conduction times QRS duration QTc interval and the mean plasma level of quinidine during the study

Spontaneous atrial cycle length decreased in 15 patients increased in four and was unchanged in two after quinidine The mean change was 77 msec (9 per cent)

A V nodal conduction time was insignificantly and variably altered by quinidine during sinus rhythm with a mean decrease of 3 msec The A H interval increased in only four patients During atrial pacing at cycle lengths from 660 to 400 msec (heart rates of 90 to 150 per minute) quinidine decreased the A H interval at comparable rates in 13 patients increased it in three and did not change it in five (Table III) At every paced cycle length the mean A H interval was shortened by quinidine Three patients developed A V nodal Wenckebach at paced cycle length of $\geq$400 msec (Table III) In addition three other patients (Nos 3 6 and 21) developed A V nodal Wenckebach at faster paced heart rates Quinidine prevented this phenomenon in one patient (No 6) delayed its onset in two patients (Nos 5 and 12) and did not change the time of its occurrence in three patients (Nos 3 11 and 21)

His Purkinje conduction time was prolonged by quinidine in 19 out of 21 patients at sinus rhythm (Table II) The mean increase was 6 msec (12 per cent) with a range of 8 to 25 per cent. The two patients whose H V interval re

Table I Clinical data

Patient	Age	Sex	Cardiac diagnosis	Indication for catheterization	Additional comments
1	39	M	ASHD	Multifocal VPC	
2	47	M	RHD	VPCs	RBBB/LAH
3	60	M	ASHD	Multifocal APC VPC paroxysmal atrial fibrillation	LBBB/LAH
4	52	M	ASHD	Conduction disturbance	RBBB/LAH
5	19	M	None	Ventricular bigeminy	
6	21	M	ASHD	Multifocal APCs paroxysmal atrial tachycardia	
7	47	M	? cardiomyopathy	VPCs	
8	42	M	ASHD ventricular aneurysm	VPCs	LAH IVCD DMI
9	63	M	ASHD	Multifocal VPC	
10	50	M	None	VPCs	
11	64	M	Cardiomyopathy ? alcoholic ? diabetic	APCs VPCs	LBBB
12	62	M	HCVD	APC VPC	LAH
13	61	M	HCVD ASHD	APCs paroxysmal atrial fibrillation	
14	55	M	ASHD	VPC	RBBB,DMI AMI
15	59	M	None	VPCs	LBBB tricyclic anti depressants
16	50	M	Alcoholic cardiomyopathy	VPCs	
17	62	M	ASHD HCVD	Angina pace	
18	64	M	ASHD	APC JPC	DMI
19	37	M	ASHD	APCs paroxysmal atrial fibrillation	
20	56	M	HCVD ASHD	APCs VPC	LAH
21	72	M	ASHD	VPCs	IVCD

Abbreviations ASHD = atherosclerotic heart disease RHD = rheumatic heart disease HCVD = hypertensive cardiovascular disease DMI = diaphragmatic myocardial infarction JPC = junctional premature contractions IVCD = intraventricular conduction defect VPC = ventricular premature contractions APC = atrial premature contractions RBBB = right bundle branch block LAH = left anterior hemiblock LBBB = left bundle branch block

A_1) and following every eighth driven beat a premature atrial depolarization (A_2) was introduced at progressively shorter A_1 A_2 intervals up to the point of atrial refractoriness

After control determinations were completed each patient received 600 to 800 mg of quinidine gluconate intramuscularly Studies were repeated 45 to 90 minutes after quinidine administration Plasma samples for quinidine determination were obtained for the control period 45 minutes following drug administration and approximately every 15 minutes thereafter to the end of the study Post drug studies were usually completed in less than 30 minutes Blood pressure measurements were obtained with a sphygmomanometer throughout the post quinidine study Care was taken to insure grounding of all equipment

Definition of terms

A H interval was used as an approximation of A V nodal conduction time and was measured from the onset of the low atrial electrogram to the onset of the His bundle deflection (normal values for this laboratory 60 to 140 msec)

His Purkinje conduction time is defined as the H V interval which is taken from the initial deflection of the His potential to the earliest point of ventricular depolarization from either the ECG leads or the intracardiac electrogram (normal values for this laboratory 35 to 55 msec)

Effective refractory period (ERP) of the atrium is defined as the longest S_1 S_2 interval at which S_2 fails to depolarize the atrium S representing the stimulus artifact

ERP of the A V node is defined as the longest A_1 A_2 interval at which A_2 fails to depolarize the His bundle

Functional refractory period (FRP) of the A V node is defined as the shortest H_1 H_2 interval that results from any A_1 A_2

ERP of the His Purkinje system is defined as the longest H_1 H interval at which H_2 fails to conduct to the ventricles

Table IV Effects of quinidine on refractory periods of the A-V conducting system*

Patient	CL	*ERP atrium*		*ERP AVN*		*FRP AVN*		*ERP HPS*		*RRP HPS*	
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	600	200	2.0			335	360			365	420
2	7.0	270	320			390	450			430	505
3	500	190	220			325	300			<3"5	315
4	700	200	250			410	400	415	400	415	420
5	650	280	300	630	400	705	.30			<705	560
6	500	230	240	260	<260	480	430				
7	700	230	270			375	385			440	475
8	600	270	280			395	400				
9	5 0	230	260	290	<285	350	465			375	405
10	550	210	230	300	290	360	370			<360	390
11	500	210	260	390	<360	4"0	4"5				
12	900	180	260	460	410	540	520			<540	530
13	550	240	240	275	<260	405	370			<405	390
14	500	240	210			330	295	<330	370	340	375
15	600	230	270	285	<275	335	335			<335	360
16	600	230	230			315	340			385	410
17	700	250	250			330	340			450	500
18	650	240	260			335	360	350	<360	400	480
19	1 000	240	"50			380	395	400	440	.10	540
20	550	240	250	295	<275	425	385			<4.5	405
21	500	240	250	320	<310	38.	370				
Mean		231	"55	351	312	399	389			400	440

All numbers in msec

quinidine and therefore no valid comparison could be made

The RRP of the His Purkinje system was prolonged by a mean of 40 msec after quinidine in all 12 patients in whom comparable measurements could be made One patient developed LBBB after quinidine when no aberration was seen prior to the drug (Fig 4)

Plasma quinidine levels Plasma quinidine levels following intramuscular administration peak in 45 to 90 minutes[38] Our studies were done during this time and the average of the quinidine level at the onset of the study at its conclusion are listed as mean values for each patient in Table II Plasma quinidine values ranged from 2 to 7 5 mg per liter with a mean of 4 6 mg per liter and at these levels extrasystoles were either abolished or markedly decreased in all patients in whom they were present prior to quinidine administration

Side effects Most patients had a small drop in systolic blood pressure averaging 10 mm Hg In no patient did the blood pressure fall more than 20 mm Hg The only other effect noted was transient nausea approximately one hour after quinidine in three patients The development of ventricular tachyarrhythmias felt to be etiologic in quinidine syncope[39-41] was not seen

Discussion

The results of this clinical study are in agreement with previous in vivo and in vitro animal experiments which have demonstrated that quinidine decreases conduction and increases refractoriness of the atrium and His Purkinje system[11-18] In most patients quinidine like procainamide caused an increase in the H V interval and prolongation of both the effective and relative refractory periods of the His Purkinje system[42,43] The explanation for the apparent shortening of the ERP of the His Purkinje system in one patient (Fig 3) is similar to that proposed for the so called Type II gap in A V conduction phenomenon[44,45] In the control period, the ERP of the His Purkinje system was determined by an area of refractoriness in the distal portion of the system Following quinidine impulses were conducted more slowly within the proximal His Purkinje system If the proximal conduction delay is sufficient to allow the distal

Table III Effects of quinidine or A V nodal conduction at various paced atrial cycle lengths*

Patient	600†		600†		550†		500†		450†		400†	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	85	110	90	110	95	125	110	135	110	140	130	150
2	110	105	120	125	130	125	130	125	140	130	155	150
3					105	85	115	90	115	95	120	100
4	90	70	100	75	115	85	125	90	160	95	180	115
5	W‡	170			W	210	W	W				
6					95	70	120	70	265	190	300	250
7	90	80	95	85	100	95	115	100	125	105	145	125
8			105	90	105	100	115	110	130	135	135	150
9			100	110	120	115	140	120	170	125	180	135
10	70	70	70	85	80	90	100	105	120	120	120	135
11	145	130	170	140	170	160	210	190	W	W		
12	W	170			W	W						
13			95	95	100	110	105	115	130	130	150	150
14			95	100	95	105	95	110	100	110	100	120
15			85	75	90	75	90	75	100	90	100	90
16			85	80	85	90	90	90	100	105	110	110
17			110	80	110	80	115	90	120	90	120	100
18	80	75	85	80	90	80	95	90	100	85	125	90
19			110	120			125	140	160	170	160	180
20			155	125	160	130	160	145	185	140	255	165
21			95	90	105	100	120	100	140	135	140	135
Mean	96	91	104	98	108	101	118	111	134	124	148	139

All numbers given in msec
†Cycle lengths at which atrium was driven
‡W = Wenckebach phenomenon

mained constant (Nos 5 and 20) had plasma quinidine levels of 7 and 3 8 mg /L , respectively Atrial pacing further altered His Purkinje con duction in only one patient (No 9) who developed rate related left bundle branch block at a cycle length of 400 msec after quinidine

QRS duration, during sinus rhythm was in creased in 11 out of 21 patients by a mean of 5 msec with a range of 5 to 15 msec The basic QRS configuration did not change in any pa tient

QTc interval was prolonged in every patient by an average of 44 msec Nine patients had ECG evidence of an infra His conduction distur bance manifested by left anterior hemiblock and/or bundle branch block prior to quinidine The effect of quinidine on the H V QRS, and QTc intervals in these patients was not different from the group as a whole

Refractory periods Analysis of the effects of quinidine on the refractory periods of the atrium A V node, and His Purkinje system is listed in Table IV

ERP of the atrium was increased by a mean of 24 msec in 17 out of 21 patients after quinidine In only one patient (No 14) did quinidine de crease the ERP of the atrium

ERP of the AVN was decreased by quinidine in all ten patients in whom it could be measured. Although the mean decrease was approximately 40 msec in one patient (Fig 1) quinidine decreased the ERP of the AVN by 230 msec In spite of this effect on the ERP of the A V node quinidine inconsistently affected the FRP of the A V node increasing it in twelve decreasing it in eight and not changing it in one patient

The ERP of the His Purkinje system could only be studied in four patients In two of these pa tients quinidine prolonged the *ERP by 40 msec.* The results from patient No 14 are shown in Fig 2 In the third patient, quinidine caused an ap parent shortening of the ERP *by 15 msec* as shown in Fig 3 (see Discussion) In a fourth pa tient who *developed block* within the His Purkinje system during control studies a com parable H_1 H_2 interval was not reached after

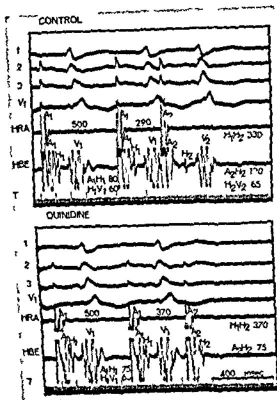


Fig 2 Prolongation of the ERP of the His Purkinje system by quinidine The patient is being paced at an atrial cycle length of 500 msec In the control tracing at an $A_1 A_2$ of 290 msec a ventricular response occurs the $H_1 H_2$ is 330 msec After quinidine at an $A_1 A_2$ of 370 msec block within the His Purkinje system occurs at an $H_1 H_2$ of 370 msec Thus the ERP of the His Purkinje system was increased by at least 40 msec Note that the $A_1 H_1$ decreased 5 msec and $H_1 V_1$ increased 5 msec after quinidine

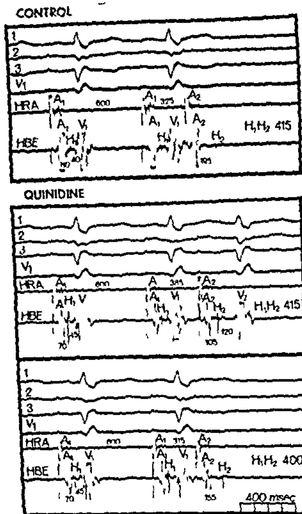


Fig 3 Apparent shortening of the ERP of the His Purkinje system by quinidine Th patient is being paced at a basic cycle length of 600 msec In the control tracing at an $A_1 A_2$ of 325 msec the resulting $H_1 H_2$ is 415 msec and block within the His Purkinje system is seen After quinidine at an $A_1 A_2$ of 385 msec the $H_1 H_2$ that results is 415 msec but the impulse conducts to the ventricles with a markedly prolonged $H_2 V$ of 120 msec At a shorter $A_1 A_2$ of 315 msec the resulting $H_1 H_2$ of 400 msec again blocks within the His Purkinje system See Discussion for explanation. Note that quinidine shortened the $A_1 H_1$ and lengthened the $H_1 V_1$ by 40 and 5 msec respectively

tened A V nodal conduction time in two thirds of the patients and either prevented or delayed the onset of A V nodal Wenckebach in half the patients exhibiting this phenomenon Furthermore in all patients in whom it could be measured the ERP of the A V node was shortened by quinidine Added to the fact that spontaneous atrial cycle length was shortened these results suggest an antivagal effect of quinidine Prior work in animals[9,23,28,46] and clinical experience in man[5,6,34] have suggested a significant anticholinergic effect of quinidine However our data cannot rule out a small contribution due to enhanced sympathetic tone in response to a small drop in blood pressure Such effects on the A V node are important for the following reasons

1 A V nodal conduction delay need not be an absolute contraindication to the use of quinidine in the management of certain arrhythmias

2 The conversion of atrial flutter from 2 1 to 1 1 conduction following quinidine[34] is not only due to decreasing the input into the A V node by slowing the flutter rate but may also be due to shortened A V nodal refractoriness and perhaps enhanced A V nodal conduction

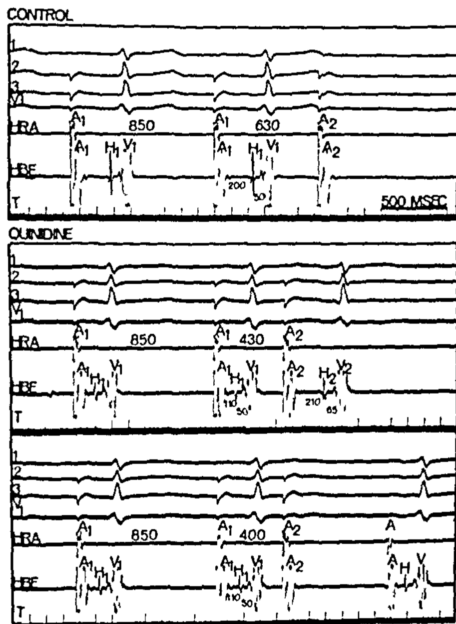


Fig 1 Effect of quinidine on the ERP of the A V node In each of the three panels from top to bottom are ECG Leads I II III V_1 high right atrial electrogram (*HRA*) His bundle electrogram (*HBE*) and time lines (*T*) All subsequent tracings will be arranged in this manner In each of the panels the patient is being paced at an A_1 A_1 of 850 msec In the control tracing one can see that at an A_1 A_2 of 630 msec A_2 fails to depolarize the His bundle thus defining the ERP of the A V node After quinidine the tracings show conduction through the A V node at an A_1 A_2 of 430 msec When A_1 A_2 is further decreased to 400 msec A blocks within the A V node Thus the ERP of the A V node was decreased 230 msec after quinidine Also note the A_1 H_1 decreased from 200 msec in the control tracing to 110 msec after quinidine The H_1 V_1 was not changed by quinidine

area of the refractoriness to recover activation of ventricular myocardium will ensue It is apparent that this response to quinidine is dependent upon the drug s ability to impair proximal conduction to a greater extent than it increases distal refractoriness

Nine patients had pre existing abnormalities in the His Purkinje conduction manifested by bundle branch block, fascicular block or prolonged H V interval Quinidine s effect on conduction and refractoriness of the His Purkinje system in these patients was of the same magnitude as in those without pre existing conduction abnormalities

Studies of the effects of quinidine on the A V node have been limited[23,28] and suggest no significant effect on A V nodal conduction Our findings during sinus rhythm are in agreement with these previous reports However, we did note that during atrial pacing quinidine shor

laboratory indicate that propranolol increases the ERP of the A V node while not affecting the refractoriness of the His Purkinje system[50]

Summary

The electrophysiological effects of intramuscular quinidine were evaluated using His bundle electrograms and the extrastimulus method. The mean mid study plasma quinidine level was 4 6 mg per liter Our results show that quinidine tends to shorten A V nodal conduction time while it routinely prolongs His Purkinje and intraventricular conduction time The refractory periods of the atrium and His Purkinje system were prolonged by quinidine while the effective refractory period of the A V node was consistently shortened. Those patients with evidence of infra His conduction disturbances manifested no difference in their response to quinidine from the group as a whole These studies suggest quinidine has antivagal properties which are of clinical significance In addition the effects of quinidine on His Purkinje conduction and refractoriness may lead to the ventricular tachyarrhythmias implicated in quinidine syncope by a re entrant mechanism

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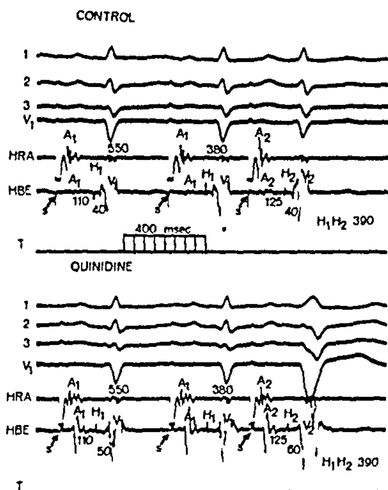


Fig 4 Effect of quinidine on the RRP of the His Purkinje system The basic paced cycle length is 550 msec and A_1 A_2 is 380 msec prior to and after quinidine Before quinidine no aberration or H V prolongation is noted at an H_1 H_2 of 390 msec After quinidine at the same H_1 H_2 of 390 msec aberration of the left bundle branch block with left anterior hemiblock is seen and the H_2 V_2 has increased 10 msec over the H_1 V_1 Thus the RRP of the His Purkinje system was prolonged by quinidine

3 The prolongation of the P R interval occasionally seen following quinidine is more likely related to its effects on His Purkinje conduction than to its effect on the A V node

4 As noted by Moe and Abildskov[8] people being treated for paroxysmal atrial tachycardia with quinidine may not respond to the usual vagal maneuvers frequently used to terminate this arrhythmia

Heissenbuttel and Bigger[30] using ECG amplification displayed at rapid speeds found a dose related increase in QRS duration and QTc prolongation in all patients taking quinidine orally and suggested that QRS prolongation more accurately defined early quinidine effect In the present study, intramuscular quinidine prolonged the QTc interval in all 21 patients while QRS duration was increased in only 11 of the 21 patients Quinidine plasma levels were similar in both studies The differences in the effects of quinidine on QRS duration for the two studies may be related to the differences in the routes of administration and the acute vs chronic nature of the studies

Comparison of quinidine to other antiarrhythmic agents The effects of quinidine on the electrophysiological properties of the A V conduction system in man are similar to those of procainamide and differ from diphenylhydantoin lidocaine and propranolol Both lidocaine[48,49] and diphenylhydantoin[43,47] shorten the ERP and RRP of His Purkinje system and do not alter His Purkinje conduction time While lidocaine has variable effects on A V nodal conduction and refractoriness diphenylhydantoin tends to shorten A V nodal conduction time and decrease the ERP of the A V node Propranolol also prolongs A V nodal conduction time while not affecting conduction through the His Purkinje system[43] Studies now in progress in our

Morphology of acute myocardial infarction in relation to coronary thrombosis

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The motivation for this study was a desire to observe the relationship between a myocardial infarct and coronary occlusion in patients with undisputed clinical and pathologic evidence of acute myocardial infarction It was hypothesized that the thrombus where found was a second ary phenomenon related to flow redistribution by the collateral vessels in the stenosed ar teries[1,2] To prove or disprove this hypothesis we conducted the following study

Materials and methods

This study was conducted in 100 consecutive cases that had objective clinical signs of myocar dial infarction that showed coagulation necrosis of the myocardium at autopsy The patients were hospitalized and died within 25 days of the onset of the disease in coronary units at either the Medical School of the University of Milan or at the Institute of Clinical Physiology of the University of Pisa Their sex and age distribu tion are shown in Table 1

After formalin fixation each heart was cut into slices 1 cm thick proceeding from the apex to within 3 cm of the atrioventricular groove Each main coronary artery and its branches were sectioned transversely at 3 mm intervals along their entire course The sliced hearts and coronary arteries were then photographed (Fig 1) The length of any segment of moderate or severe coronary artery stenosis was measured.

From the I t tut Anatom Patolog c Un ers ty of M lan and the I t tuto di Fis logia Clinica, Un versity di Pisa, Pisa, Italy

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The area of acute infarction and the total area of each slice were measured from the photographs using a polar planimeter and the percentage of the total volume of the left ventricle undergoing coagulation necrosis was calculated from this data Histological sections were used to deter mine the edges of the infarct in assessing the af fected area The volume percentage of scar tissue when present was also calculated sepa rately in this way

Histological studies (hematoxylin and eosin and Movat and PAS stains) were made of many samples of myocardium taken from normal bor derline and necrotic portions of each slice An average of 20 blocks per heart were examined. In each heart all segments of coronary artery and branches that showed from moderate to severe stenosis or occlusion were also examined histologically A total of 296 segments were studied According to the method previously de scribed,[1] the average diameter of the residual lumen was measured with a micrometer and the percentage of luminal narrowing was calculated with reference to normal lumen of the vessel.

To assess the incidence of thrombosis with respect to various morphologic variants (which may have a different functional significance) the following classifications were devised

I *Age of myocardial infarct* (coagulation necrosis)

(A) *Early infarct* in which death was esti mated to occur within two days of the onset of the necrotic myocardial lesion and was characterized by eosinophilia stretching of the muscle fibers and edema with early polymorphonuclear cell infiltrates (Fig 2A B)

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Fig 2 A through D Different patterns of coagulation necrosis. *A* Early focal infarct. *B*, Early confluent infarct. *C*, Acute massive infarct. *D* Recent massive infarct (*A* *C* *D* hematoxylin and eosin. *B* PAS stain *A*, *B* original magnification × 50 *C*, *D* original magnification × ?0)

IV *Type of coronary stenosis* A stenosing plaque was defined as

(A) *Fibrous* when connective tissue prevailed whether or not it contained small amount of lipids (Fig 3*A*)

(B) *Atheromatous*, when it showed true massive atheroma (Fig 3*B*)

Correlative studies were made between the incidence of coronary thrombosis and the following age size type and location of the infarct degree length and histological characteristics of coronary stenosis pre existing myocardial scarring heart weight anticoagulant therapy and terminal shock

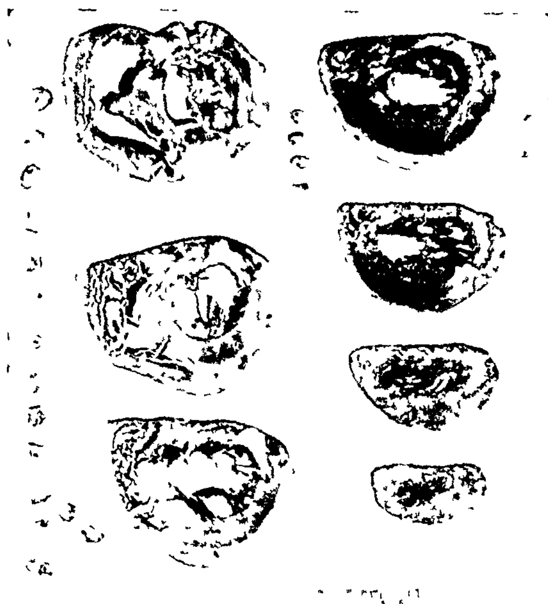


Fig 1 Example of a sliced heart showing a 10 day old infarct involving 46 per cent of the left ventricular mass

(B) *Acute infarct* from three to ten days old (extensive infiltration and subsequent lysis of polymorphonuclear leukocytes increased edema changes in small vessels with wall degeneration and thrombosis and early reaction at the margin of the infarct (Fig 2C)

(C) *Recent infarct* from 11 to 25 days old (early collagen deposition to incomplete fibrous repair) (Fig 2*D*)

II *Type of myocardial infarct (coagulation necrosis)* The type of infarct was defined as

(A) *Massive* when all the cells of the infarcted zone with a maximum diameter greater than 5 mm underwent coagulation necrosis (Fig 2C, D)

(B) *Confluent* when multiple necrotic foci tended to join together with some separation of the foci by apparently viable myocardium (Fig 2*B*)

(C) *Focal* when the lesions appeared as unique or multiple microfoci of coagulation necrosis, scattered in normal tissue (Fig 2*A*)

III *Location of myocardial infarct (coagulation necrosis)* Infarcts were said to be

(A) *Subendocardial* when limited to the internal one fourth of the cardiac wall

(B) *Internal* if they involved the inner half of the wall

(C) *External* if they involved the outer half or

(D) *Transmural* if they extended from epicardial to endocardial surface

Table II Frequency of coronary thrombosis related to size and age of infarction

	Per cent infarct								
	<10	11-20	21-30	31-40	41-50	>50	Total	M	F
TOTAL INFARCTS									
Occlusive thrombus	4	7	10	5	9	3	38	26	12
Mural thrombus	4	6	8	2	2	—	22	15	7
No acute occlusion	21	7	7	4	1	—	40	25	15
Total	29	20	2[illegible]	11	12	3	100	66	34
EARLY INFARCTS									
Occlusive thrombus	2	—	1	2	—	—	5	4	1
Mural thrombus	2	2	3	—	—	—	7	6	1
No acute occlusion	15	4	—	1	—	—	20	13	7
Total	19	6	4	3	—	—	32	23	9
ACUTE INFARCTS									
Occlusive thrombus	—	2	8	2	5	2	19	12	7
Mural thrombus	2	2	5	—	—	—	9	[illegible]	4
No acute occlusion	4	1	3	2	—	—	10	5	5
Total	6	5	16	4	5	2	38	22	16
RECENT INFARCTS									
Occlusive thrombus	2	[illegible]	1	1	4	1	14	10	4
Mural thrombus	—	2	—	2	2	—	6	4	2
No acute occlusion	2	2	4	1	1	—	10	7	3
Total	4	9	5	4	7	1	30	21	9

P rcentag f the total v lume of the left tricle und rgoi g coagulation necrosis.

11 33 and 23 respectively Again the type of in farct correlated with its increasing age

Table IV shows that the frequency of thrombi did not differ in cases where the infarct was transmural or internal External infarcts were found in only two instances One had a mural thrombus and the other no acute occlusion No occlusive thrombi were detected in the 12 suben docardial infarcts In only 3 cases a small mural thrombus was observed. Of these 12 cases 8 showed an early focal infarct 3 confluent (2 early 1 recent) and only one an acute massive infarct. In all these cases the infarct size was within 10 per cent.

The degree of stenosis in a supplying artery is related to the incidence of thrombosis in Table V All but three arteries with mural thrombi had a stenosis greater than 70 per cent at the site of the thrombus Occlusive thrombi were invari ably located in a vessel at a site where the lumen was more than 70 per cent stenosed. The lumen of arteries that were not acutely occluded ranged from a normal diameter to more than 90 per cent stenosed. More precisely in 4 cases (2 early 1 acute and 1 recent) no lumen reduction was noted while in 3 other cases (1 early 1 acute and 1 recent) the stenosis was less than 50 per cent. In these cases the infarct was suben docardial in 3 with a size less than 10 per cent and transmural in 4 with a size less than 10 per cent and transmural in 4 with a size ranging from 16 to 33 per cent.

Table VI shows an increased frequency of thrombi with an increasing length of old luminal stenosis

Among the 40 cases without acute coronary occlusions a total of 53 main arterial vessels were judged to supply the infarcted area In

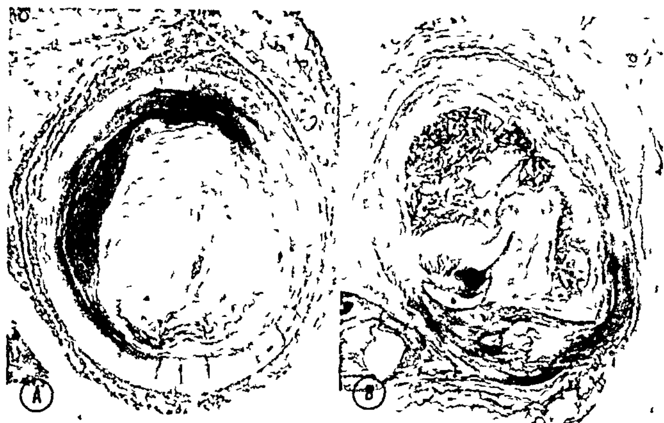


Fig 3 A and B Different types of arterio atherosclerotic damage *A* severe coronary stenosis mainly due to fibrous deposition *B* Severe atheromatous coronary stenosis

Table I Sex and age frequency of cases studied

	Age range (yr)					
	30 39	*40-49*	*50 59*	*60 69*	*>70*	*Total*
Males	1	10	13	27	15	66
Females	—	3	5	14	12	34
Total	1	13	18	41	27	100

Results

Thirty eight of the 100 cases showed a throm bus that completely filled the residual lumen at the site of severe stenosis of a main subepicar dial arterial coronary vessel tributary to the in farcted zone No occlusive thrombus was found in the remaining 62 cases However in 22 of these a small thrombus was found generally overlying an atherosclerotic plaque This tiny 'mural' thrombus did not significantly reduce the vessel lumen In two instances the mural thrombus was seen in a stenotic lumen of a vessel not tributary of the infarcted myocar dium

Table II shows that the incidence of occlusive or mural thrombi increases with the increasing size of the infarction It must be noted that the size of an infarct correlated with its increasing age as we defined them

The incidence of thrombosis is related to the type of infarct in Table III The frequency of both occlusive and mural thrombi is higher in massive infarcts and less in confluent infarcts No case with focal infarct showed an occlusive thrombus In addition out *of 15 focal infarcts* 12 were early, 2 acute and 1 recent the 18 con *fluent infarcts* were early in 9 instances acute in 3, and recent in 6, the 67 massive infarcts were

Table II Frequency of coronary thrombosis related to size and age of infarction

	Per cent infarct								
	<10	*11 20*	*21-30*	*31-40*	*41-50*	*>50*	*Total*	*M*	*F*
TOTAL INFARCTS									
Occlusive thrombus	4	7	10	5	9	3	38	26	12
Mural thrombus	4	6	8	2	2	—	22	15	7
No acute occlusion	21	7	7	4	1	—	40	25	15
Total	29	20	25	11	12	3	100	66	34
EARLY INFARCTS									
Occlusive thrombus	2	—	1	2	—	—	5	4	1
Mural thrombus	2	2	3	—	—	—	7	6	1
No acute occlusion	15	4	—	1	—	—	20	13	7
Total	19	6	4	3	—	—	32	23	9
ACUTE INFARCTS									
Occlusive thrombus	—	2	8	2	5	2	19	12	7
Mural thrombus	2	2	5	—	—	—	9	5	4
No acute occlusion	4	1	3	2	—	—	10	5	5
Total	6	5	16	4	5	2	38	22	16
RECENT INFARCTS									
Occlusive thrombus	2	5	1	1	4	1	14	10	4
Mural thrombus	—	2	—	2	2	—	6	4	2
No acute occlusion	2	2	4	1	1	—	10	7	3
Total	4	9	5	4	7	1	30	21	9

P centage of th total olum of the l ft ventr le underg i g coagulation ecrosis.

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Table IV shows that the frequency of thrombi did not differ in cases where the infarct was transmural or internal External infarcts were found in only two instances One had a mural thrombus and the other no acute occlusion No occlusive thrombi were detected in the 12 subendocardial infarcts In only 3 cases a small mural thrombus was observed. Of these 12 cases, 8 showed an early focal infarct 3 confluent (2 early 1 recent) and only one an acute massive infarct. In all these cases the infarct size was within 10 per cent.

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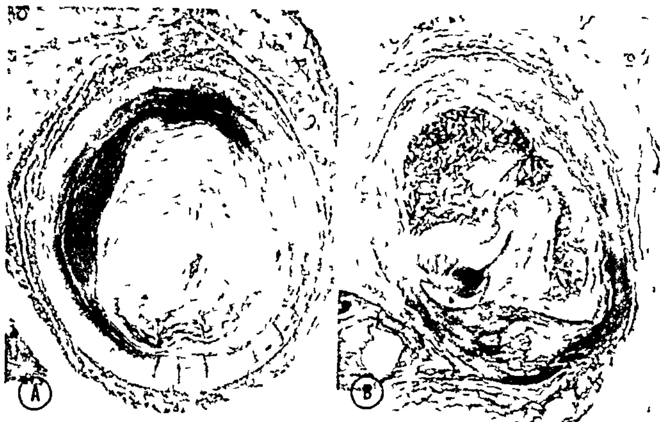


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TOTAL INFARCTS									
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Total	29	20	25	11	12	3	100	66	34
EARLY INFARCTS									
Occlusive thrombus	2	—	1	2	—	—	5	4	1
Mural thrombus	2	2	3	—	—	—	7	6	1
No acute occlusion	15	4	—	1	—	—	20	13	7
Total	19	6	4	3	—	—	32	23	9
ACUTE INFARCTS									
Occlusive thrombus	—	2	8	2	5	2	19	12	7
Mural thrombus	2	2	5	—	—	—	9	5	4
No acute occlusion	4	1	3	2	—	—	10	5	5
Total	6	5	16	4	5	2	38	22	16
RECENT INFARCTS									
Occlusive thrombus	2	5	1	1	4	1	14	10	4
Mural thrombus	—	2	—	2	2	—	6	4	2
No acute occlusion	2	2	4	1	1	—	10	7	3
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Table III Frequency of thrombosis related to size and type of infarction

	Per cent infarct						
	<10	11 20	21-30	31-40	41 50	>50	Total
MASSIVE							
Occlusive thrombus	1	6	8	5	9	3	32
Mural thrombus	1	4	7	2	2	—	16
No acute occlusion	2	5	7	4	1	—	19
CONFLUENT							
Occlusive thrombus	3	1	2	—	—	—	6
Mural thrombus	1	1	1	—	—	—	3
No acute occlusion	7	2	—	—	—	—	9
FOCAL							
Occlusive thrombus	—	—	—	—	—	—	—
Mural thrombus	2	1	—	—	—	—	3
No acute occlusion	12	—	—	—	—	—	12
Total	29	20	25	11	12	3	100

Table IV Frequency of thrombosis related to size and location of infarction

	Per cent infarct						
	<10	11 20	21 30	31 40	41 50	>50	Total
TRANSMURAL							
Occlusive thrombus	1	1	4	4	8	2	20
Mural thrombus	1	3	7	1	2	—	14
No acute occlusion	5	5	4	4	1	—	19
INTERNAL							
Occlusive thrombus	3(-)	6	6	1	1	1	18
Mural thrombus	3(3)	2	1	1	—	—	7
No acute occlusion	16(9)	2	2	—	—	—	20
EXTERNAL							
Occlusive thrombus	—	—	—	—	—	—	—
Mural thrombus	—	1	—	—	—	—	1
No acute occlusion	—	—	1	—	—	—	1
Total	29	20	25	11	12	3	100

Subendocardial infarcts

these the coronary stenoses were mainly fibrotic in 24, atheromatous in 29 hemorrhage was observed in atheroma of the latter cases in 11, while in three the morphological appear ance suggested rupture of the atheromatous plaque

Of the 38 supplying vessels in patients with an acute occlusive thrombus eight showed a fibrous stenosis 30 an atheromatous stenosis In 16 of the latter there was a hemorrhage in the atheromatous plaque and in three ' rupture of an atheroma In the group of 22 cases with mural thrombosis the figures were 4 18 3 and 6 respectively

Table V Frequency of thrombosis related to per cent of pre existing lumen stenosis and size of infarction

Per cent old lumen reduction in supplying artery	*Per cent of infarcted myocardium*						
	<10	*11 -0*	*21 30*	*31-40*	*41 50*	*>50*	*Total*
<70							
Occlusive thrombus	—	—	—	—	—	—	—
Mural thrombus	1	—	2	—	—	—	3
No acu e occlusion	5	2	2	3	—	—	12
70							
Occlusive thrombus	1	2	4	2	1	1	11
Mural thrombus	2	2	3	—	1	—	8
No acute occlusion	5	2	2	1	—	—	10
80							
Occlusive thrombus	3	3	2	1	4	1	14
Mural thrombus	—	—	2	2	1	—	5
No acute occlusion	3	1	3	—	1	—	8
>90							
Occlusive thrombus	—	2	4	2	4	1	13
Mural thrombus	1	4	1	—	—	—	6
No acute occlusion	8	2	—	—	—	—	10
Total	29	20	25	11	12	3	100

A myocardial scar preceding the terminal infarct was present in 62 cases In 44 individuals its size excluding the size of the acute infarct, was less than 10 per cent *of the total left* ventricular mass in 14 between 11 per cent and 30 per cent and in four cases it *was greater than* 30 per cent In 28 instances the scar was subendocardial in 20 internal and in 14 transmural. The type of scar was focal in 23 confluent in 28 and massive in 11 In 31 cases the scar was located within the acutely infarcted area in 16 within the normal myocardium and in 15 in both No correlation could be found between the presence and/or size of a scar and the incidence of occlusive coronary thrombosis

A more or less pronounced increase of the heart weight was observed in many of the present cases (Table VII) The 40 individuals in whom the blood pressure values prior to the infarct were known 15 had a diastolic pressure higher than 90 mm Hg In the latter group eleven were females with a heart weight ranging from 300 to 560 Gm average 428 Gm and six were males the heart weight of whom ranged from 430 to 850 Gm average 646 Gm In the remaining 25 cases, the 19 males showed values ranging from 350 to 720 Gm average 492 Gm and six females from 400 to 480 Gm, average 455 Gm No relation was noted between heart weight, size of infarct and the incidence of thrombosis.

Anticoagulant therapy was used in 70 cases In them the frequency of occlusive thrombus was 37 per cent (mural thrombus in 28 per cent) Occlusive thrombi were found in 39 per cent of the remaining 30 individuals who did not have anticoagulant therapy (mural thrombus in 19 per cent)

Occlusive thrombi could be demonstrated in 38 per cent of the patients who had terminal irreversible shock and in 40 per cent of those who did not

Discussion

In the present series despite a similar fatal clinical course the morphology of the myocardial lesion showed a widespread variety as to size type and location of the coagulation necrosis concerned. In particular the two factors size and type" correlated with the age of the infarct maximal values being found mainly in cases with a longer survival This is in keeping

Table VI Frequency of thrombosis related to length of pre existing stenosis

Per cent old lumen reduction in supplying artery	Length old stenosis (mm.)				
	<10	11 20	21-30	>30	Total
<70					
Occlusive thrombus	—	—	—	—	—
Mural thrombus	1	1	—	1	3
No acute occlusion	11	—	1	—	12
70					
Occlusive thrombus	1	2	2	6	11
Mural thrombus	2	1	2	3	8
No acute occlusion	2	4	2	2	10
80					
Occlusive thrombus	3	1	5	5	14
Mural thrombus	1	—	—	4	5
No acute occlusion	4	2	1	1	8
>90					
Occlusive thrombus	1	2	3	7	13
Mural thrombus	—	3	2	1	6
No acute occlusion	5	2	3	—	10
Total	31	18	21	30	100

Table VII Frequency of thrombosis related to heart weight

	Heart weight (Gm.)					
	<290	300-399	400-499	500-599	>600	Total
Occlusive thrombus	—	5	19	7	7	38
Mural thrombus	1	4	4	9	4	22
No acute occlusion	—	8	16	7	9	40
Total	1	17	39	23	20	100
Males	—	8	24	16	18	66
Females	1	9	15	7	2	34

with the concept that the evolution of experimental coagulation necrosis starts as scattered microfocal lesions and may progressively enlarge to a confluent or massive involvement of the myocardium[3,5] Apparently at any step in this evolution death may ensue following conduction disturbance and/or cardiac failure At present, therefore there is no reason to consider the different morphologic stages as the result of different processes as claimed by those who believe that only the large infarcts are true infarcts[6,7] This claim was established by the authors because they observed the highest frequency of occlusive thrombi associated with the largest infarcts However in the present series if only those cases with an infarct size greater than 10 per cent are selected of 71 cases 34 (47 8 per cent) showed an occlusive thrombus An occlusive thrombus was present in 27 (52 9 per cent) of 51 cases with an infarct size greater than 20 per cent, in 17 (65 3 per cent) of 26 cases with an infarct size greater than 30 per cent in

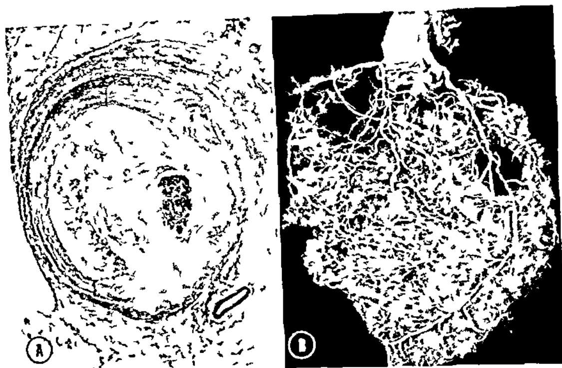


Fig 4 A and B Comparison between the histologic feature of an occluded severe stenosis by a thrombosis and the plastic cast view in presence of a severe stenosis *A* Old severe stenosis with a thrombus occluding the residual lumen *B* Plastic cast of the arterial coronary tree showing a severe stenosis of the anterior descending branch (*within the black circle*) The distal portion of the stenosed vessel is injected by numerous enlarged anastomoses. (*A* Movat stain. *A* Original magnification × 13)

12 (80 per cent) of 15 cases with an infarct size greater than 40 per cent and in all three cases with a size greater than 50 per cent Our data make it correct to state that in patients dying within 25 days of the onset of a myocardial infarction an acute thrombotic coronary artery occlusion coexisting with the myocardial infarction is a relatively infrequent finding (38 per cent of cases) a datum also demonstrated in vivo by coronary angiograms[8] The wide range (from 7 to 96 per cent) in incidence of occlusive coronary thrombi reported in the literature[7,9] may be explicable on the basis of the selection of the examined material In fact the frequency of an occlusive thrombus in our data shows a clear correlation with the increasing severity of the following morphologic changes

(1) *Size of the infarct* This in turn seems to correlate with type and age of the infarct. In other words infarcts of minor size were mainly early and focal while with an increasing survival time the infarct size progressively increased to confluent or massive coagulation necrosis Subendocardial infarcts were in general early and focal this may explain why no occlusive thrombi were found (see above) However our data show that even transmural infarcts have a low incidence of associated occlusive thrombi (20 [48 per cent] out of 53 cases)

(2) *Degree length, and type of the stenosis.* In all cases in which a thrombus was present, the degree of old stenosis in the vessel where the thrombus was located was judged higher than 70 per cent It could be argued that we do not have a precise method at present for the histological valuation of the lumen reduction However the method we employed allows an acceptable approximation when classifying the progressive degree of stenosis Furthermore the incidence of thrombi in our data increased with an increasing length of stenosis. Finally because experimental results have shown that the normal fibrinolytic activity of the vessel wall in atherosclerotic rabbits is so reduced that coronary thrombi induced by intracoronary thrombin infusion do not disappear as they do in the

normal animal,[10,11] a distinction has been made between "atheromatous" and "fibrotic" plaques This was done to assess if a relationship could be established between thrombi and either of these conditions Thirty of the 38 occlusive thrombi proved associated with "atheromatous" plaque In our series intimal hemorrhage or rupture of atheroma were not important associated factors Other factors such as previous myocardial scarring weight of the heart, anticoagulant therapy, or terminal irreversible shock apparently do not influence, *per se* the frequency of the thrombus

From our data it seems legitimate to state that the thrombus when present generally occurs at the level of an "atheromatous" stenosis with marked lumen reduction over a long vessel segment

In the present series 7 per cent of the cases had an infarct (even large and transmural) without acute occlusions and without significant lumen reduction Indeed, some had practically normal coronary arteries or wall changes with normal lumen or only a short stenosis of the supplying branch with a lumen reduction less than 50 per cent Another 55 per cent had an infarct without occlusion but with one or more severe vascular stenoses while in 38 per cent of the infarcts an occlusive thrombosis was associated with severe lumen reduction This means that in most instances one or more silent stenoses were present a long time before the clinical onset of the disease and therefore the myocardium was apparently already well supplied by enlarged collaterals[2,12]

The present data thus confirm the earlier findings giving a further support to the following previous suggestions[1,2,1] first that a coronary thrombosis has little if any role in reducing the nutrient flow to the area of myocardium supplied by a severely stenosed vessel (Fig 4) This supposition was substantiated by the lack of infarct and/or ventricular fibrillation after the occlusion of an experimental coronary stenosis had lasted for several days[13] Second, that the thrombus could be a secondary phenomenon since the preexisting collateral backflow determines a critical hemodynamic situation at the level of severe stenosis Factors which influence this critical situation can cause a thrombus Actually the likelihood of thrombus formation is maximal in the presence of a "large" and "massive" infarct In this condition the blockage of the intramural flow in the necrotic area—due to loss of contraction with stretching of the cardiac wall interstitial edema, thrombosis of the small vessels, etc, secondary to coagulation necrosis[2] is maximal resulting in an increased peripheral resistance with further stasis at the level of the coronary stenosis Stasis in the supplying artery of an infarcted myocardial area has been experimentally documented[14] This hemodynamic factor associated with increased coagulability following tissue necrosis and with decreased fibrinolytic activity of the fibro atheromatous vessel wall are factors that support the assumption that the thrombosis is a secondary event.

The same pathogenetic mechanism may cause the late worsening of an obstructive lesion In fact when a stenosis reaches the critical point in which reduction of proximal flow is counterbalanced by distal collateral backflow, the deposition of mural thrombus may be enhanced (encrustation theory of Rokitansky) and lead to a progressive reduction of the vascular lumen Recent observations in patients with aortocoronary saphenous vein grafts show that the bypassed coronary stenoses may occlude after a relatively short time[15] Possibly the flow through the vein graft produces a situation analogous to that determined by the previously mentioned collateral backflow

From a morphological standpoint there is no objective proof that a myocardial infarction in man is caused by an acute coronary occlusion[12,16] This conclusion is supported by a recent epidemiologic study in which the increased tendency of the myocardium to infarction is not related to an increased prevalence of atherosclerosis or an increased tendency to intravascular thrombosis[17]

Summary

The relationships between the following were examined in 100 patients who died within 25 days after presenting with clinical and pathological evidence of a myocardium infarction frequency of acute coronary occlusion, degree and length of old fibrous atheromatous stenosis at the site of eventual coronary occlusion, size type and location of the infarct size of pre existing scars weight of the heart irreversible shock and anticoagulant therapy

In 62 cases no acute occlusive lesion was present while in 38 cases an occlusive thrombus was found always located at the site of an old severe stenosis. The presence of the thrombus correlated with the increasing size of the infarct the increasing length of the pre existing stenosis The present findings support the hypothesis that the thrombus is a secondary phenomenon related to flow redistribution by collateral vessels in stenosed arteries

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Arrhythmias induced by exercise in paced patients

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Although it is generally known that complete heart block may revert to regular sinus rhythm after a period of pacing little is known about other types of spontaneous ventricular activity that can occur with exercise A recent study by Singer and associates[1] indicated that 76 per cent of patients with implanted pacemakers developed new rhythms of varying types during exercise This observation was of such importance that we felt it was necessary to repeat the study ourselves with specific attention given to history of previous spontaneous ventricular contractions and to the relationship of these arrhythmias to the type of pacemaker either fixed rate or non competitive

If arrhythmias proved to be frequent it would suggest that there should be more careful selection of pacemaker mode We have held for example, that whenever possible fixed rate pacemakers should be used because they will last much longer than pacers with sensing circuits This advantage has usually been weighed *against the supposed danger of inadvertent* stimulation of the heart during the vulnerable period of the T wave For this reason, first pacemaker implants have been typically non competitive units until the patient s electrocardiogram could be observed on numerous occasions over the ensuing years. When a patient revealed no evidence of arrhythmia or competition, fixed rate pacemakers were selected as the replacement unit. Based upon a survey of pacemaker users in the United States in 1970, most physicians must have agreed with this concept because non competitive pacemakers were overwhelmingly chosen for permanent pacing [2]

Materials and methods

Forty eight patients from a series of approximately 500 were selected for this study Most were selected on the basis of absence of competition over a number of years All of our patients are observed in a pacemaker clinic on the average of six times a year, where among other observations the electrocardiogram as displayed on an oscilloscopic monitor and on a paper rhythm strip is observed *Any single spontaneous ventricular contraction* during that period is reported as competition—yes' on the computerized report Patients were considered free of 'competition" if all the units were tagged as 'competition—no' during the entire follow up period that averaged 4 7 years The patients tended to be younger than the group average which now is approximately 70 years so that exercise could be more easily accomplished There were 30 men and 18 women ranging in age from 17 to 82 years with an average age of 62 years They had been paced for an average of 4 7 years ranging from seven months to 12 years

Indications for original pacemaker implanta

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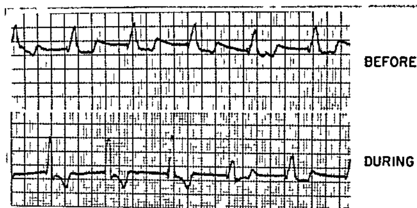


Fig 1 77 year old man complete heart block with Cordis Stanicor (ventricular inhibited pacemaker) During exercise beats 1 2 and 3 reveal accelerated ventricular rhythm

tion were complete heart block in 28 patients intermittent complete block in 16 (two with atrial fibrillation) second degree A V block in three and sick sinus syndrome in one (Table I) With respect to etiology 42 patients had either arteriosclerosis or heart disease of undetermined etiology Four patients had congenital A V block one associated with corrected transposition of the great vessels One patient had complete heart block following viral myocarditis One patient had complete A V block surgically induced by ligation of the A V node for intractable supraventricular tachycardia

Endocardial pacing was done in 43 patients and myocardial (epicardial) in five Fixed rate pacemakers were implanted in 13 patients and non competitive pacemakers in 35 (ventricular inhibited 14 ventricular triggered 21) Pacemaker dependency defined as a slow ventricular rate likely to produce syncope should the pacemaker fail abruptly was identified at the time of the first implantation and during replacement of the pulse generator Twelve of 13 patients with fixed rate pacemakers were considered pacemaker dependent, as were 24 of 35 patients with non competitive pacemakers Twenty five of the 28 patients with complete A V block were considered pacemaker dependent as were eight of 16 patients with intermittent complete block and three with second degree heart block

During observation in the pacemaker clinic competition was never detected in 23 patients (eight with fixed rate units) occasionally in 23 patients and often in two patients (Table II) Nineteen of the 23 patients that never competed before were pacemaker dependent, as were 16 of 23 with occasional competition and one of the two with frequent competition

Table I Indications for original pacemaker implantation in 48 patients

Indication of pacemaker	*Fixed rate*		*Non-competitive*	*Total*
Complete heart block	10		18	28
Intermittent complete heart block	2		14	16
Second degree A V block	1		2	3
Sick sinus syndrome	0		1	1
	—		—	—
Total	13	+	35	48

Method

The exercise test was performed in the pacemaker clinic where emergency equipment including an external defibrillator was available An electrocardiogram was recorded either through a standard patient cable or through a telemeter that transmitted to a nearby receiver The treadmill was set at slow speed at a slope of 15 degrees The speed was increased gradually until the patient became tired or until a satisfactory record was obtained (usually 1 5

Four of th fi e pat nts with epicardi l wires h d been pa ed fo s x to 12 years Transth r c i sertion f pacem k rs h s ot been practiced i our I c s nce 1966 w th th e eption of the one patient whose A V nod was lig ted

P ovided through the c urtesy of Mennen-G e tb tch Buffalo N Y

Table II Observations of 48 patients in pacemaker clinic

Type of arrhythmia	Competition prior to exercise test			
	Never competed	Occasional competition	Usual competition	Total
Complete heart block	16	12	0	28
Intermittent complete heart block	6	9	1	16
Second degree A V block	1	2	0	3
Sick sinus syndrome	0	0	1	1
Total	23	23	2	48

Table III Rhythm disturbances in 38 patients

Prior competition	Competition linked to exercise
Never	18/23 (69 5%)
Occasional	18/23 (69 5%)
Usual	2/2 (100%)
Total	38/48 (79%)

to 2 0 miles per hour for approximately four minutes) The electrocardiographic Lead II was selected on the basis of clarity of the P wave and freedom from somatic tremor The most frequent leads were Lead II a V_R or Marriott Lead MCL A recording was made for a full minute before exercise during the entire exercise period and after the exercise until the pre exercise rhythm returned usually within five to seven minutes In three instances it was necessary to repeat the test at a later date because of imperfection in the electrocardiographic record Two patients were monitored for additional 12 hour periods on a Holter counter

Results

The test was well tolerated in all cases All arrhythmias were self limited and usually disappeared after a short period of rest None of the patients complained of chest pain, but many were fatigued and short of breath Only two were aware of palpitations

Rhythm disturbances appeared in 38 patients (79 per cent) (Table III) In patients that never competed before, spontaneous ventricular beats were seen in 18 of 23, in 18 of 23 that competed occasionally, and in both the patients who had shown frequent competition

Four of the eight patients with fixed rate pacemakers who had never competed before developed competing rhythms (Table IV) Of the 15 patients with non competitive pacemakers who had never competed before 14 developed competing rhythms

Various types of spontaneous ventricular activity were observed (Table V) Normal A V conduction appeared in six patients Four of them had complete heart block and had never been known to exhibit competition before One of these was in a patient with a fixed rate pacemaker and three with non competitive units Junctional (or high nodal) rhythm was observed in 16 patients in six as isolated premature beats and 10 in form of short bursts of junctional tachycardia Ventricular premature beats were detected in 27 patients There were short runs of ventricular tachycardia in three patients all with non competitive pacemakers two of whom had never been known to compete before Multiple arrhythmias were seen in 14 patients with non competitive pacemakers and in eight competition had never been observed. Some typical examples are shown in Figs 1 to 5

The timing of some of the arrhythmias was such that pacing impulses often fell on the apex of the T wave of the preceding ventricular beat This was seen in four patients with fixed rate pacemakers (two with no prior competition) and in one patient with a ventricular triggered

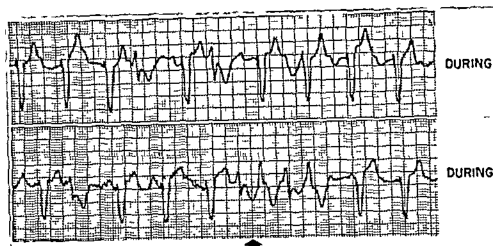


Fig 2 28 year-old woman complete heart block with Medtronic ventricular inhibited pacemaker During exercise there was bigeminy and at arrow is a short run of paroxysmal ventricular tachycardia

Table IV Number and percentage of patients with competing rhythms

Pacemaker mode	*Exercise arrhythmia/prior competition*			
	Never	*Occasional*	*Usual*	*Total*
Fixed rate	4/8 (50%)	2/5 (40%)	0/0	6/13 (46%)
Non competitive	14/15 (93%)	16/18 (88%)	2/2 (100%)	32/35 (91%)

pacemaker without prior competition The R on T phenomenon was detected in one patient with a ventricular triggered pacemaker The three instances of runs of ventricular tachycardia were *not* associated either with spike on T or R on T phenomena

Discussion

The frequency of the occurrence of new rhythms during exercise in patients with implanted pacemakers was high 79 per cent, which compared almost precisely with the report by Singer and colleagues[1] This figure was particularly striking because in this series patients were selected on the basis of no prior competition (48 per cent) and were *not* chosen at random from our series Actually 86 per cent of *consecutively* selected patients have demonstrated competition and one would assume that exercise would elicit competing rhythms in most of them. In the *selected* group chosen for this study half of the patients with fixed rate pacers without prior competition showed competing mechanisms including one patient whose A V node had been ligated.

Table V Type of spontaneous ventricular beats with exercise

Rhythm	*Number*
Normal A V conduction	6
Junctional premature contraction	
Isolated	6
Coupled or repetitive	10
Ventricular premature contraction	
Isolated	25
Coupled	2
Ventricular tachycardia	3
Multiple in same patient	14

It is not possible to judge whether competition in this series of patients is serious or represents a significant risk but one might suspect it to be

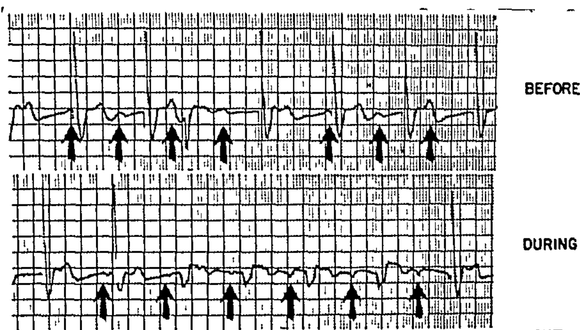


Fig 3 67 year old man complete heart block Cordis Stanicor (ventricular inhibited) pacemaker During exercise NSR supervened with Wenckebach sequence of the A V node

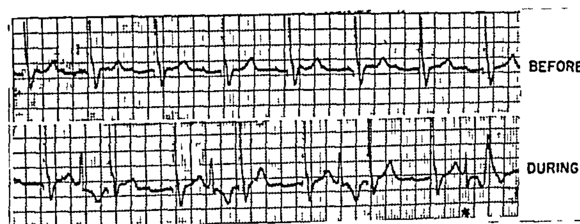


Fig 4 33 year old woman with ligation of A V node and Cordis Ventricor (fixed rate) pacemaker During exercise there are coupled beats of junctional origin and after asterisk there is a beat of ventricular origin falling on the T wave of the previous complex

less safe than no competition at all There has been no agreement in the literature on the dangers of competition For example we have found that most of the sudden deaths in our series of patients occurred in patients with fixed rate pacemakers [3] This observation was also made by Sowton [4] On the other hand Furman and Escher [5] Zoll and colleagues [6] Chardack and co workers [7,9] and Meltzer and Kitchell,[8] based on data of their own, have disagreed with this conclusion It has been our belief that competition between naturally occurring cardiac contraction and a fixed rate pacemaker represents a small risk Whether or not exercise, fatigue, catecholamine secretion, myocardial infarction or anoxia will seriously increase the danger is a matter of conjecture Certainly although two of our patients were aware of palpitations there were no serious side effects either during the test or during vigorous activity, and no arrhythmias were actually triggered by the pacemaker impulse

Should frequent competition effect our choice of a pacemaker? This decision requires a trade off between the alleged dangers of competition and the benefit of prolonged pacemaker life that can be attained with a fixed rate unit. (It should be noted that a non competitive pacemaker does not guarantee that there will be no stimulation on the apex of the T wave as occurred in one of

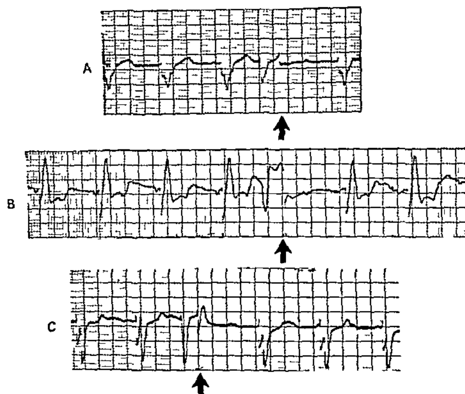


Fig 5 A through C Three separate examples of spontaneous ventricular activity in patients with fixed rate pacemaker that never before demonstrated spontaneous ventricular activity A 61 year old man paced for 11 years Arrow shows ventricular premature contraction with the pacemaker stimulus falling on the T wave B, 46 year-old woman with similar findings. C 56 year old woman with similar finding In no case did the stimulus on the T wave produce repetitive firing or ventricular tachycardia

our patients This occurs when there is a short coupling interval with a pacemaker with a relatively long refractory period.) Whether or not one concludes that competition is dangerous there is general agreement that patients with frequent competition are more comfortable with non competitive than with fixed rate pace makers[10] Moreover if there is the slimmest chance that dangerous arrhythmias might be triggered by pacing on the T wave why not use a pacemaker that will usually avoid this even tuality?

The results of this study suggest the following conclusions

1 Selection of the type of permanent pace maker to implant. Fixed rate units should be used only in patients who have never demonstrated competition This observa tion should be confirmed by an exercise test.
2 No matter what mode of pacing the lower the electrical output of the pacer the less danger there would be of stimulation on the T wave Consequently effort should be *made to use low output pacemakers*
3 The refractory period of a non competitive pacemaker should be relatively short in order to detect extra systoles with short coupling intervals
4 Patients who wish to engage in vigorous ex ercise while wearing implanted pace makers should have exercise tests to evalu ate the possibility of serious *arrhythmias* Any patient complaining of palpitations during routine daily activities should be monitored during exercise
5 Patients with fixed rate pacemakers who develop frequent competition with exercise should have their pacemakers replaced with non competitive units

Summary

Seventy nine per cent of a series of 48 patients with implanted pacemakers developed arrhyth

mias during exercise There were 23 patients without known previous competition and in 69 5 per cent of them arrhythmias developed during exercise

No serious arrhythmias developed, but there were three cases of repetitive firing or short bursts of ventricular tachycardia five instances of pacing on the apex of the T wave and one instance of R on T phenomenon *None* of these cases of ventricular tachycardia was preceded by spike on T or R on T stimulation

Based on these observations recommendations for selection of the proper pacemaker have been made

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Systemic and coronary hemodynamic effects of sodium nitroprusside

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Treatment for hypertensive crises with sodium nitroprusside was reported[1-4] many years ago and it was shown to be rapidly effective in controlling various hypertensive states including the hypertension induced by pheochromocytoma after phentolamine was no longer effective[5] Its systemic hemodynamic effects were studied in man and its hypotensive action was confirmed[6] However it was not used widely at least partly because of its toxicity[7-9] There has been wide recent clinical interest[10-13] in the use of the drug however and its hemodynamic effects have been restudied in subjects with coronary artery disease or cardiomyopathy[14] and its renal effects were studied in hypertensive subjects[15] and in the dog[16] The data obtained previously in dogs[1] and man[6,14,15] did not include observations concerning coronary blood flow and myocardial metabolism This seems of critical importance in hypotensive subjects Therefore the present study was done

Methods and materials

Ten mongrel dogs averaging 25 1 ± 2 9 kilograms in weight were anesthetized by subcutaneous administration of 3 mg per kilogram of body weight of morphine sulfate followed one hour later by intravenous administration of 0 25 ml per kilogram of body weight of a mixture of equal parts of veterinary pentobarbital and Dial urethane* In the hour succeeding the establishment of anesthesia two cardiac catheters were manipulated fluoroscopically into the pulmonary artery one into the coronary sinus and one into the right atrium A needle was inserted percutaneously into the left femoral artery and two needles were placed in the right femoral artery A cuffed endotracheal tube was attached through a non rebreathing valve to a Tissot spirometer for air collection and to a two way valve so the dog could breathe room air during the determination of cardiac output or a mixture of 15 per cent nitrous oxide 21 per cent oxygen and 64 per cent nitrogen during the determination of coronary blood flow Cardiac output was measured by the Fick principle with air collection over a five minute period as well as by the indicator dilution method subsequent to injection of indocyanine green dye into the pulmonary artery Indicator was sampled through the femoral artery utilizing a Gilson dye tracer writing on a Gilson macropolygraph Expired air was analyzed with the Scholander apparatus for oxygen and carbon dioxide The oxygen content of blood from the femoral and pulmonary arteries and the coronary sinus was determined by the Van Slyke Neill apparatus Duplicate samples were required to check within 0 2 ml /100 ml of blood. The pH of systemic arterial and coronary sinus blood was determined with the Radiometer Microelectrode Type E5021A Hemoglobin was determined with the Coleman Jr spectrophotometer Coronary blood flow was measured by the nitrous oxide saturation technique assuming the partition coefficient of 1 between

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*Dial urethane contains D al (di allyl barb turic cid) 100 mg /ml mono ethylurea 400 mg /ml and ur th e 400 mg /ml. Veterinary pe toba bital contains 60 mg /ml. of pe tobarb tal

blood and myocardium The nitrous oxide content of arterial and coronary sinus blood was determined by the method of Orcutt and Waters Various hemodynamic parameters were calculated by standard formulas as previously described Cardiac output was measured by indicator dilution curves once during the determination of cardiac output by the Fick principle and once during the measurement of coronary blood flow There was close agreement between the cardiac outputs determined by dye and Fick method, therefore all three of these determinations of cardiac output were averaged for the control observations and its calculations Three similar determinations of cardiac output during the infusion of sodium nitroprusside were used for calculating the experimental observations

The plan of study was as follows cardiac output and coronary blood flow were determined at rest Sodium nitroprusside was then infused through a peripheral vein in the foreleg at the rate of 8 mcg per kilogram of body weight per minute As seen in the graphs cardiac output was determined by indicator dilution curves immediately prior to the onset of the infusion of nitroprusside and again 2½ 6 14 and 19 minutes after the infusion was begun The Fick cardiac output was measured beginning five minutes after the onset of infusion of sodium nitroprusside and coronary blood flow was determined from 10 to 20 minutes after the onset of the infusion The infusion was then discontinued and five minutes after the termination of the infusion, cardiac output was determined again by the indicator dilution method In Table I is presented the control observations made by the Fick and dye method and the observations by the Fick and dye method after the acute effects (Graph I) had subsided and during the prolonged infusion of sodium nitroprusside In the graph are plotted the hemodynamic parameters as calculated from indicator dilution curves and Fick output obtained during the control period the dye curves immediately prior to the onset of the infusion, and those 2½, 7½ and 12½ minutes after the onset of the infusion, and finally, the dye curve five minutes after the infusion was discontinued

Results

During the infusion of sodium nitroprusside as seen in Table I, cardiac rate increased while blood pressure decreased in the right atrium pulmonary, and systemic arteries The minute volume of respiration increased, accompanied by slight but not significant increases in oxygen consumed and carbon dioxide exhaled while the body respiratory quotient was unchanged. The mixed venous oxygen content rose with significant narrowing of the arteriovenous oxygen difference Cardiac output was significantly increased, and total peripheral and pulmonary resistances were decreased Cardiac work rose acutely but then decreased and over all throughout the sustained effects of the infusion, was not significantly different from the control

During the sustained infusion coronary blood flow was significantly increased with a considerable reduction in coronary vascular resistance The coronary sinus oxygen content increased slightly but significantly with a significant reduction in the arterio coronary sinus oxygen difference and a significant increase in left ventricular oxygen utilization

The graphs are constructed from the data collected by indicator dilution curves and therefore reflect transient events more closely than does Table I They reveal that peripheral and pulmonary resistance decreased rapidly with the onset of the infusion of sodium nitroprusside accompanied by an increase in heart rate and cardiac output Similarly there was a transitory increase in cardiac work when the infusion began but as the infusion continued and the arterial pressure decreased cardiac work returned again to control values Most parameters tended to return toward the control value after the infusion was discontinued

Discussion

It is interesting that the decrease in vascular resistance produced by sodium nitroprusside is manifested not only in the systemic arterial bed but also in the lung and in the myocardium This is what might be expected from a drug acting directly on the smooth muscle in the vessel wall Nitroprusside relaxes smooth muscle from the uterus and intestine and reduces the vascular resistance in several isolated perfused vascular beds of animals [7] Relaxation of smooth muscle in the veins could contribute to the reduced central venous pressure seen here

The left ventricular oxygen consumption increased more percentage wise (Table I) than did

Table I Dogs with sodium nitroprusside—control to study

Parameter	*Control ± S D*	*Study ± S D*	*% change*	*P value*
Heart rate (beats/minute)	89 ± 17	104 ± 9	+ 16 9	< 0 01
Mean arterial blood pressure (mm Hg)	117 ± 17	108 ± 12	− 7 7	< 0 05
Mean pulmonary artery blood pressure (mm Hg)	17 ± 2	15 ± 2	− 11 8	< 0 001
Mean right arterial blood pres ure (mm Hg)	7 3 ± 1 3	5 2 ± 1 4	− 28 8	< 0 001
Arterial hematocrit (%)	40 6 ± 6 0	41 7 ± 5 7	+ 2 7	< 0 2
Arterial oxygen content (ml /100 ml of blood)	16 4 ± 2 3	16 8 ± 2 5	+ 2 4	< 0 2
Δ Arterial mixed venous oxygen (ml /100 ml of blood)	3 9 ± 1 0	3 2 ± 1 0	− 17 9	< 0 05
Coronary sinus oxygen content (ml /100 ml of blood)	6 0 ± 2 1	7 8 ± 2 8	+ 30 0	< 0 001
Δ Arterial-coronary sinus oxygen (ml /100 ml of blood)	10 5 ± 2 0	9 1 ± 2 4	− 13 3	< 0 02
Oxygen consumption (ml./minute)	124 ± 28	131 ± 35	+ 5 6	< 0 1
Body respiratory quoti nt	0 96 ± 0 09	0 96 ± 0 07	—	—
Cardiac output (L./minute)	3 13 ± 0 64	4 06 ± 1 30	+ 29 7	< 0 05
Stroke volume (ml)	36 ± 5	39 ± 10	+ 8 3	< 0 5
Left ventricular work (Kg M /minute)	5 1 ± 1 5	6 0 ± 2 3	+ 17 6	< 0 1
Right ventricular work (Kg M./minute)	0 7 ± 0 2	0 8 ± 0 2	+ 14 3	< 0 2
Total peripheral resistance (c.g s. units)	3082 ± 634	2296 ± 394	− 25 5	< 0 01
Total pulmonary resistance (c g s units)	452 ± 117	330 ± 93	− 27 0	< 0 001
Coronary blood flow (ml /100 Gm /minute)	97 ± 29	148 ± 38	+ 52 6	< 0 001
Coronary vascular resistance (units)	1 29 ± 0 35	0 78 ± 0 25	− 39 5	< 0 001
Left ventricular oxygen usage (ml./100 Gm /minute)	10 0 ± 2 5	13 2 ± 4 0	+ 32 0	< 0 05
Cardiac respiratory quotient	0 91 ± 0 08	0 88 ± 0 07	− 3 3	< 0 4

In th data prese ted here cardiac output is th a e age of one d termination by the Fick principle and two by the indicator dilut on method (see text) Coronary blood fl w was measured by th nitrous o id method.

the heart rate and may not be entirely attributable to the rate change The sum of the per cent increase in rate and the per cent increase in left ventricular work (even though the latter did not reach statistical significance except transiently) are adequate to explain the observed increase in left ventricular oxygen consumption In spite of the greater cardiac oxygen consumption how ever the coronary sinus oxygen content in these normal animals increased This leads one to believe that myocardial oxygenation is improved since a change in the oxygen content of the venous effluent is generally believed to reflect the direction of a change in tissue oxygenation It is not reasonable to presume that the same im provement would occur in subjects with coro nary atherosclerosis which caused localized restriction of myocardial blood flow Under these

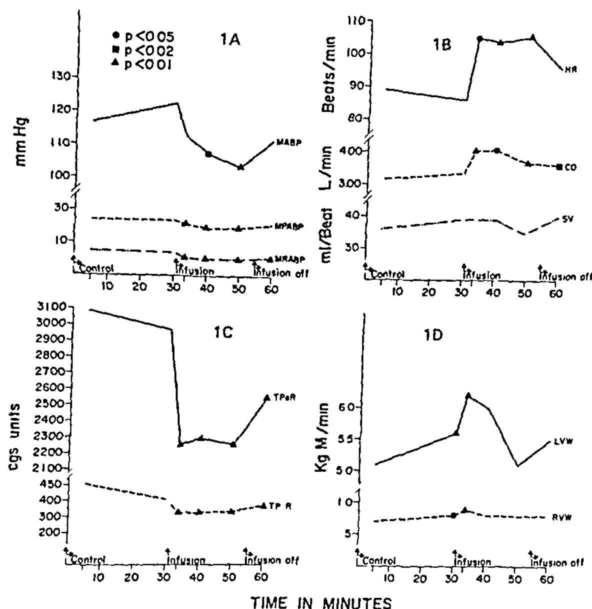


Fig 1 A through D Figure 1 presents hemodynamic parameters determined before during and after the intravenous infusion of a solution of sodium nitroprusside at a rate of 8 mcg /kg /min The time scale is presented along the abscissa for each diagram and the point in the experiment is indicated by the arrows. On each panel are presented the control measurements obtained during the initial cardiac output and coronary blood flow measurement the data just before the onset of infusion that 2½ minutes after the onset of the infusion the set of data collected during the second Fick output and measurement of coronary blood flow and finally the observations made five minutes after discontinuing the infusion The key for the statistical significance of observations as determined by the t test for paired values is indicated in the upper left of panel *A* Units are indicated along the ordinate of each graph and the parameter in question is indicated at the right hand end of each line In panel *A* *MABP* = mean systemic arterial blood pressure measured from the femoral artery *MPABP* = mean pulmonary arterial blood pressure *MRABP* = mean pressure in the right atrium In panel *B*, *HR* = heart rate *CO* = cardiac output in liters/minutes *SV* = stroke volume in ml In panel *C*, *TPeR* = total peripheral resistance in dynes cm $^{-5}$ seconds *TPuR* total pulmonary resistance in dynes cm $^{-5}$ seconds In panel *D* *LVW* left ventricular work *RVW* right ventricular work

circumstances the increase in cardiac rate and the trend toward increase in left ventricular work might produce myocardial ischemia and it would seem proper to look for such a response if subjects with known angina pectoris are given this agent to control hypertensive crises

Summary and conclusions

I The systemic and coronary hemodynamic effects of an infusion of sodium nitroprusside has been studied in anesthetized mogrel dogs.

II Sodium nitroprusside reduced vascular resistance in the systemic pulmonary, and cor

onary circuits while cardiac output and coronary blood flow increased

III There was an increase in mixed venous and coronary sinus blood oxygen content with narrowing of the arteriovenous oxygen difference across both systemic and coronary vascular beds consistent with improved tissue oxygenation

IV When the nitroprusside infusion was discontinued there was prompt reversal of the decrease in vascular resistance with a rise in systemic arterial pressure an increase in systemic vascular resistance and a decrease in heart rate

V Although these hemodynamic responses encourage one to expect a favorable response in those with labile vascular resistance caution is urged for those who may have generally labile vascular resistance but fixed resistances which cannot change in the coronary or other vascular beds

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Cardiopulmonary volumes and blood volume expansion in experimental acute myocardial infarction with and without shock

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With the significant reduction in mortality rate from acute myocardial infarction (AMI) achieved from improved recognition and treatment of complicating dysrhythmias attention has become more sharply focused on meeting the more formidable challenge of pump failure complicating AMI The syndrome of cardiogenic shock in particular has continued to prove resistant to medical therapy with the mortality rate remaining in the 80 to 90 per cent range

Blood volume expansion has periodically been recommended in the treatment of AMI either with or without shock The results of earlier clinical studies of blood or plasma infusions in cardiogenic shock were reviewed along with their own results by Binder and associates[1] and judged to be of doubtful benefit More recently low molecular weight dextran has been used in AMI with and without shock again with variable effects on ultimate survival [2-5]

The rationale for blood volume expansion in AMI involves two premises (1) that in AMI there may be a total or compartmental reduction of blood volume, and (2) that regardless of blood volume reduction or redistribution the acutely infarcted left ventricle is capable of responding effectively to an added volume load in terms of Frank-Starling performance

In some patients with AMI hypovolemia may be present as a result of vomiting prior diuretic or catecholamine administration or other less well defined factors,[6] but measured total blood volumes in AMI with or without shock have varied [7-10] It has been suggested that in the absence of a reduced total blood volume in such patients reduced stroke volume might be related to decreases in effective or central blood volume resulting in inadequate left ventricular filling Measurements of central blood volume in AMI have not clearly supported this concept either in uncomplicated AMI or cardiogenic shock [8,10-12] Measurements of left ventricular (LV) end diastolic volume have to date been absent from studies of such patients

In the dog studies on cardiopulmonary volumes in experimental AMI and the effects of blood volume expansion are even more limited In experimental cardiogenic shock total blood volume has been found to be reduced quite late in the course[13,14] in agreement with one study in humans [7] Following AMI in non shock animals true cardiopulmonary volume (right atrium to aortic root) has been found by us to be unchanged[15] while reported effects on LV end diastolic volume have varied [15-17] In a single study including blood volume expansion in experimental AMI in dogs low molecular weight dextran infusions appeared to potentiate the effects of catecholamines [18]

In the present study we determined the effects

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of AMI with shock and without shock on hemodynamics and cardiopulmonary volumes in closed chest anesthetized dogs We also subjected these damaged hearts to volume loads including those that might be used clinically and compared the response to those obtained in normal dogs In order to avoid any secondary peripheral effects of the infusate on viscosity we restricted the fluid administered to donor dog blood.

Methods

Successful studies were performed in 55 mongrel dogs anesthetized with morphine sulfate (3 mg per kilogram of body weight) and sodium pentobarbital (15 to 20 mg per kilogram of body weight) and placed in the right lateral decubitus position Cuffed endotracheal tubes were inserted and respiration was assisted by means of a Harvard volume type respirator to assure adequate ventilation[19] verified by determinations of arterial pH and Po_2 Catheters were advanced under fluoroscopy via neck and femoral vessels to the left ventricle aortic root, right atrium and pulmonary artery with ECG monitoring

Statham transducers (P23Db) placed at midthoracic level were used for measurement of pressures which were averaged during the course of a respiratory cycle Indicator dilution determinations of cardiac output true cardiopulmonary blood volume and LV end diastolic volume (indocyanine green) were made as described in earlier reports from this laboratory[20-22]

Dye curves pressures and electrocardiograms were recorded on an Electronics for Medicine DR 8 recorder

Values for cardiac output, cardiopulmonary blood volume and LV end diastolic volume were expressed per kilogram of body weight Systemic resistance (R_s) was calculated in units from the formula $R_s = Ao \times 100/CI$ where Ao is the mean aortic pressure and CI the cardiac index in ml per kilogram of body weight per minute Total pulmonary resistance (R_p) units were calculated from the formula $R_p = PA \times 100/CI$ where PA is the mean pulmonary artery pressure and pulmonary arteriolar resistance (R_a) from the formula $R_a = (PA - LVEDP)(100)/CI$ where $LVEDP$ is the left ventricular end diastolic pressure[23] As an estimate of changes in myocardial oxygen consumption a pressure rate index (product of systolic aortic pressure heart rate and ejection time) was calculated[24] LV minute work (MWI) in Gm M / per kilogram of body weight per minute was calculated from the formula $MWI = CI \times (LVs - LVEDP) \times 1\,36/100$ where LVs is the left ventricular systolic pressure and 1 36 the mercury correction factor

Following control measurements in 35 dogs either the left anterior descending or circumflex branch of the left coronary artery was obstructed by means of a thrombus producing electrode catheter advanced fluoroscopically 1 to 2 cm beyond the vessel s origin[25] Following obstruction as indicated by ST segment elevation in appropriate leads and the appearance of ventricular extrasystoles these dogs (MI–no shock group) were observed for two to three hours after which time hemodynamic measurements were repeated. Catheters were thereafter kept patent by flushing with heparinized saline LV end diastolic volume was determined in 14 of these dogs and cardiopulmonary volume in 12 Ventricular extrasystoles which occurred early after ischemia were eliminated by administration of intravenous procainamide (initial dose 10 mg per kilogram of body weight) none of which was required after the first hour of ischemia[26]

Blood volume was expanded in 18 dogs with multiple transfusions of donor dog blood in three ranges I (5 to 8 ml per kilogram of body weight) II (14 to 16 ml. per kilogram of body weight) and III (25 to 30 ml per kilogram of body weight) Fifteen to twenty minutes after each transfusion (infusion rate 48 ml per minute) hemodynamic measurements were repeated. The effect of these transfusions in the infarct dogs was compared to those in six normal dogs given equivalent amounts of blood A total of 68 infusions were performed in the infarct dogs and 25 in the normals

In 14 dogs following control measurements cardiogenic shock was produced by a modification of the method of Agress and associates[27] whereby one to four 40 mg boli of styrene divinylbenzene microspheres (300 micradiameter) were suspended in heparinized blood and injected through a single end hole Sones catheter into either one or both main left coronary artery branches Cardiogenic shock herein defined included both (1) at least a 33 per cent

Table I Hemodynamic effects of acute myocardial infarction (Mean ± SEM)

	HR beats/min	$\bar{A}o$ mm Hg	LVEDP mm Hg	CI ml/kg/min	Rs units	Rp units	CPV_I ml/kg	E F Percent	EDV_I ml/kg	MWI Gm M/kg/min
NON SHOCK DOGS (n=35)										
Control	129	114	6	128	89	11	14 8	30	4 3	226
	±6	±4	±1	±7	±6	±1	±0 8	±2	±0 6	±15
MI	134	112	12	78	153	22	16 7	13	4 4	126
	±5	±4	±1	±6	±12	±2	±1.3	±1	±0.5	±11
P value	NS	NS	<0 001	<0 001	<0 001	<0 001	NS	<0 001	NS	<0 001
SHOCK DOGS (n=14)										
Control	135	113	4	127	99	10	17 7	26	3 5	180
	±7	±4	±1	±13	±10	±1	±1 3	±2	±0 3	±18
MI	134	64	12	48	157	34	18 4	13	4 2	48
	±7	±4	±2	±6	±17	±8	±1 6	±1	±0 6	±7
P value	NS	<0 001	<0 01	<0 001	<0 01	<0 01	NS	<0 001	NS	<0 001
MI NO SHOCK VS MI-SHOCK (P value)	NS	<0 001	NS	<0 01	NS	NS	NS	NS	NS	<0 001

Abbreviations HR = heart rate $\bar{A}o$ = mean aortic pressure LVEDP = left ventricular end diastolic pressure CI = cardiac index Rs = systemic resistance R_p = total pulmonary resistance CPV_I = cardiopulmonary volume index E F = LV ejection fraction EDV_I = LV end diastolic volume index MWI = LV minute work index MI = myocardial infarction.
P values > 0 05 listed as not significant (NS)

reduction in aortic systolic pressure and (2) a systolic aortic pressure below 90 mm Hg persisting at least one half hour following injection Thus marked systolic hypotension was present in this group (Mean 75 ± SEM 4 mm Hg) LV end diastolic volume was determined in 11 dogs, cardiopulmonary volume in 10 and volume expansion carried out in three

Student s t test was used for statistical analysis of the data The grouped t test was used for comparison of groups the paired t test for changes within groups (i e following myocardial infarction and blood volume expansion)

Results

The effects of AMI with and without shock are compared in Table I In the non shock group following AMI there were significant increases in LVEDP systemic and pulmonary vascular resistance and reduction in cardiac index LV ejection fraction and minute work index Similar directional changes occurred in the shock group but in these when compared to the non shock group, there were statistically significant greater reductions in cardiac output and minute work as well as a reduction in aortic pressure In neither group was cardiopulmonary volume or LV end diastolic volume significantly different from controls

The effect of blood volume expansion in the normals and the non shock AMI group is compared in Table II and Figs 1 and 2 Table II represents an analysis of the effects of different levels of blood volume expansion in the normals and non shock infarct group In both groups intravascular and intracardiac pressures rose with transfusions Cardiac and minute work indices rose in the infarct group but not in the normals, but these increases were accompanied by a rise in the pressure rate index. There was a tendency for systemic and pulmonary arteriolar resistances to fall in the infarct group while they tended to remain unchanged in the normals following transfusions Heart rate tended to fall in the normals while it remained unchanged among the infarct dogs The difference in heart rate between the two groups was significant only at the third level of blood transfusion (P < 0 02)

In Figs 1 and 2 cardiac index and LV minute work are plotted against LVEDP before and

Table II Effect of blood volume expansion in normals and myocardial infarction without shock (Mean ± SEM)

	HR beats/min.	$\overline{Ao}$ mm. Hg	LVEDP mm. Hg	$\overline{PA}$ mm. Hg	RA mm. Hg	CI ml/Kg/min.	Rs units	Rp units	R_{Pa} units	MWI Gm. M/Kg/min	PRI
NORMALS (n=6)											
C	127 ±17	112 ±10	5 ±1	14 ±2	2 ±0.5	118 ±5	94 ±7	9 ±2	8 ±1 6	206 ±27	2 660 ±210
I	115 ±11	125 ±11	7 ±1	16 ±2	3 ±0 5	118 ±12	108 ±7	10 ±2	7 ±0 6	238 ±38	2 640 ±420
II	112 ±11	125† ±9	7† ±1	15† ±1	4 ±1	105 ±8	120† ±6	10 ±1	8 ±0 9	195 ±32	2 330 ±350
III	109 ±10	139‡ ±9	12‡ ±3	20‡ ±2	5‡ ±0.5	131 ±11	109 ±5	8 ±2	6 ±0 9	269 ±40	2 980 ±490
MYOCARDIAL INFARCTION (n=18)											
C	136 ±5	107 ±5	13 ±2	16 ±2	3 ±1	73 ±6	160 ±14	24 ±3	6 ±1	108 ±10	2 340 ±120
I	129 ±5	112 ±5	18† ±2	17 ±2	4† ±1	78 ±5	153 ±11	26 ±3	4† ±0 6	120 ±12	2 630 ±130
II	131 ±4	125† ±5	24‡ ±2	20 ±2	6‡ ±1	100‡ ±10	136 ±10	21 ±3	4 ±0 6	159 ±24	2 940† ±170
III	137 ±6	118‡ ±8	2[illegible]‡ ±3	23† ±3	6‡ ±1	106‡ ±9	129 ±12	24 ±3	4 ±0 6	167† ±22	3 110† ±270

Abbreviations $\overline{PA}$ = mean pulmonary artery pressure RA = right atrial pressure Rp = pulmonary arteriolar resistance PRI = pressure rate index, C = control before blood infusion I = blood infused equals 5 to 8 ml/Kg body weight II = blood infused 14 16 ml./Kg III = blood infused 25-30 ml./Kg other abbreviations as in Table I.

* = P < 0 05

† = P < 0 01

‡ = P < 0 001

after blood transfusions Within the normal range of LV end diastolic pressure (< 12 mm Hg) although the values for cardiac index and LV minute work index are reduced among the infarct dogs, the response to volume infusions was not significantly different from the normals as indicated by the similar slopes of the regression equations Despite somewhat slower heart rates among normals the same results were obtained when stroke work and stroke volume indices were plotted against LVEDP Beyond the normal range of LVEDP the response of cardiac index and LV minute work was flat with increasing LVEDP in the infarct dogs as were the results obtained plotting these variables against LV end diastolic volume

Fig 3 demonstrates the effects of cardiogenic shock and blood transfusions in three individual dogs. Blood transfusions elevated both aortic pressure and minute work in these dogs although the effects on cardiac index were variable

Discussion

In the present study true cardiopulmonary volume and LV end diastolic volume were not found to be significantly changed from controls after AMI in both shock and non shock dogs. Regarding possible total blood volume changes, the period of study was probably too short to allow for any major changes in this although it was not measured.

In the experimental animal LV volume following myocardial infarction depends upon the preparation used and the time elapsed following the myocardial ischemic injury With repeated coronary embolizations with lycopodium spores every 20 to 30 minutes Wong and associates[16] found increases in LV end diastolic volume up to 200 per cent of control or more Regan and co workers[17] found approximately a 50 per cent in

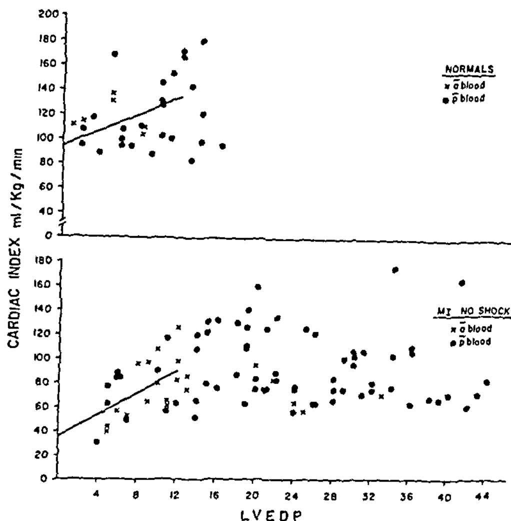


Fig 1 Effect of blood infusions in normal dogs and those with acute myocardial infarction (non shock) Although cardiac indices are reduced among the infarct dogs within the normal range of LVEDP (≲ 12 mm Hg) the slope line representing the regression equations for the infarct dogs (y = 37 03 + 4 51x) is not significantly different from that of the normals (y = 97 11 + 3 14x) x = values before transfusions • =values after transfusions

crease after one hour of acute ischemia produced with intracoronary thrombosis as described here However as in a previous report,[15] we could not detect a significant difference in LV end diastolic volume from controls two to three hours post ischemia This time was allowed to elapse in the non shock group in order to avoid any possible hemodynamic effects of the ad ministered procainamide The shock group were not given this medication to avoid any phar macologic potentiation of the hypotension Since multiple microsphere injections were usually re quired to obtain persistent marked hypotension with 20 to 30 minute intervals between injec tions, the point in time at which they were studied was roughly comparable to that used for the non shock group (½ hour after shock or 1½ to 2½ hours after the initial bead injection) The presence of previous scar may also influence the effect of acute ischemia with increased end diastolic volume found in dogs with heart failure and decreases in dogs with shock [17]

The response of normal and infarct dogs to moderate blood volume expansion differed. The insignificant changes in performance among normals was not unexpected in view of previous work demonstrating that among intact normal dogs large volume increments (50 to 70 ml per kilogram of body weight) are necessary for well defined increases in left ventricular output and work [28]

The basis for improvement in Frank Starling function among the infarct dogs probably is re lated to the presence of normally functioning myocardium and the absence of ventricular di latation Thus while the infarcted area of the ventricle may be stiffer than normal at this stage (normal volume with high end diastolic pressure) diastolic volume increments can be translated into increased output and work by the remaining functional myocardium The flat appearance of the curves beyond the normal

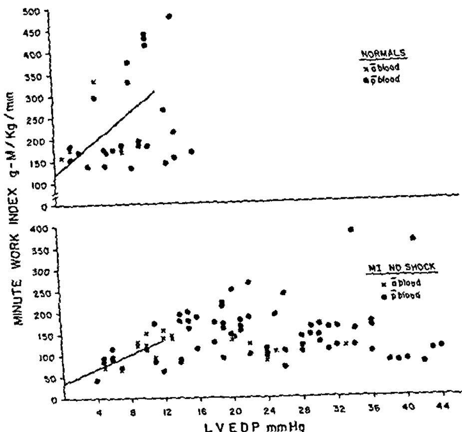


Fig 2. Effect of blood infusion in normal dogs and those with acute myocardial infarction (non shock). Although LV minute work indices are reduced among the infarct dogs within the normal range of LVEDP (≤12 mm Hg) the slope line representing the regression equation for the infarct dogs ($y = 37.32 + 8.23x$) is not significantly different from the normals ($y = 121.87 + 15.46x$). x = values before transfusions. • = values after transfusions.

levels of LVEDP is not in itself abnormal and resembles the shape of the curves obtained by Sarnoff and Berglund[29] at higher LV filling pressures in normal dogs.

The mechanism by which this altered response to moderate volume loading occurs is not clear. Alterations in peripheral resistance as a controlling factor in cardiac performance have been postulated under varying situations.[30] Although the changes are small, the decreases in systemic and pulmonary arteriolar resistance among the infarct dogs were directionally different from that of the normals and suggest that perhaps through reduced resistance to ventricular ejection cardiac performance was improved among the infarct dogs. Another possibility is preferential distribution of the transfusate to the central circulation. The blood transfusions given were selected to result in a range approximately from 8 to 30 per cent of canine total blood volume (85 to 90 ml. per kilogram of body weight).[31] When percentage increases in cardiopulmonary and left ventricular volumes after the infusions in the infarct dogs were calculated (20 to 70 per cent), they indicated that a greater proportion went to the central circulation vis a vis the blood volume as a whole. Finally, the lack of any slowing of heart rate and the decrease in systemic resistance among this group after volume loading suggest a sympathomimetic influence.

The effects of moderate blood volume expansion in AMI cannot be interpreted as wholly beneficial from the present study. The rather high LV end diastolic pressures obtained indicate the potential threat for pulmonary congestion and edema. The increased pressure rate indices indicate increased oxygen requirements which must be balanced off against the improved ventricular performance observed. In regard to

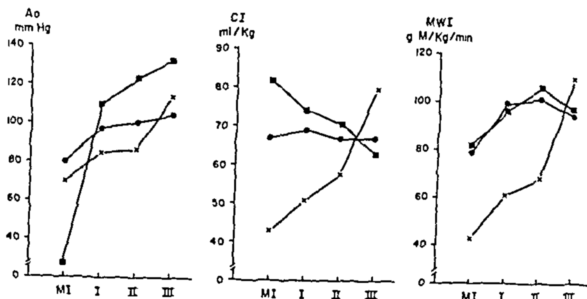


Fig 3 Effects of blood volume expansion on mean aortic pressure (*Ao*) cardiac index (*CI*) and LV minute work index (*MWI*) at three levels indicated for three individual dogs with cardiogenic shock

the shock dogs the number infused with blood was too small to draw any firm conclusions although arterial pressure and minute work rose in all three

To what extent do these canine preparations mimic AMI as it occurs in man? Main vessel obstruction to produce myocardial infarction in the non shock dogs is not far removed from the pathology found in many AMI patients at autopsy and the pressure, flow and resistance changes are similar to those reported in studies of patients with acute myocardial infarction without shock [32] Although the injection of microspheres has been used by many investigators to produce a cardiogenic shock model in our opinion it still leaves much to be desired As in human cardiogenic shock a large mass of muscle is unquestionably damaged [33] but in man shock may be imposed upon the setting of an initial or repeat infarction [33,34] and the hemodynamics of myocardial infarction with hypotension might be quite variable[35] although usually more depressed than uncomplicated myocardial infarction [34] In our hands the method also resulted in a high immediate mortality rate (approximately 80 per cent) when stringent levels of hypotension were sought Of interest however, was the finding of significantly greater decreases in cardiac index and LV work among the shock group as was reported by Hamosh and Cohn[1] in their study of LV function in shock and non shock patients with acute myocardial infarction

We used donor dog blood in this study in order to observe the effects of blood volume expansion alone The use of low molecular weight dextran clinically may offer additional hemodynamic advantages because of reduction in blood viscosity and reversal of cellular aggregates during low flow states [36,38] Recent short term acute hemodynamic studies with infusions of low molecular weight dextran in human AMI have generally revealed improvement in Frank Starling function in both uncomplicated AMI[39] and cardiogenic shock [10,40,42] However as in the dog considerations of timing and underlying differences in pathology are also likely to influence heart volumes and hemodynamics in human AMI The lack of physiologic data to enable proper patient selection and evaluation may account for the variability of results of this treatment as reported in earlier clinical survival studies Proper selection and monitoring of patients should enable future determinations of the indications for and effects of this therapy on both the mortality and morbidity rates of AMI

Summary

The effects of acute myocardial infarction on hemodynamics and cardiopulmonary volumes were studied in two groups of anesthetized closed chest dogs a non shock group (intracoronary thrombus obstruction) and a shock group (intracoronary microspheres) Moderate blood volume expansion was carried out with donor dog blood and the effects were compared with those in a group of normal dogs

The shock dogs had greater decreases in cardiac output and left ventricular work than the non shock group In neither were true cardiopulmonary volume or LV end diastolic volume increased over controls at two hours With moderate blood volume expansion improvement in Frank Starling performance occurred in the infarct dogs with no significant changes in cardiac output or work among the normal dogs

In experimental myocardial infarction blood volume expansion therefore improved cardiac performance independent of prior reductions in ventricular or central blood volume as a result of infarction However such benefits must be weighed against the threat of pulmonary edema with rising LV end diastolic pressures and possible increased oxygen costs accompanying the increases in cardiac output and left ventricular work

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Anaerobiosis induced by isoproterenol and glucagon in the presence of restricted coronary inflow

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Isoproterenol has been recommended in the treatment of low perfusion states because of its twofold effect of reducing systemic vasoconstriction and providing a potent inotropic stimulus to the myocardium[1-6] However prolonged administration especially in the presence of obstructive coronary artery disease often leads to deterioration of cardiac function presumably due to markedly increased oxygen consumption[7-10]

Glucagon has been shown to possess positive chronotropic and inotropic effects, even in the presence of beta adrenergic blockade and full digitalization[11-14] Because blood pressure is well maintained, and the incidence of arrhythmia is low glucagon has been proposed as major therapy for hypotension and heart failure[15-19]

The purpose of this study is to evaluate some of the hemodynamic and metabolic effects of these drugs in the dog in the presence of reduced coronary flow

Materials and methods

Mongrel dogs of both sexes weighing between 18 and 25 kilograms were anesthetized with 20 to 25 mg per kilogram of body weight intravenous sodium thiopental intubated and respiration was maintained with a Harvard dual phase control respirator pump Inspired oxygen concentration rate and depth of respiration were varied to maintain arterial pH Po_2 and Pco_2 within the normal range Lead II of the electrocardiogram was continuously monitored Polyethylene catheters were inserted into the femoral vein and artery and were advanced to the level of the right atrium and thoracic aorta for administration of saline and drugs and for pressure measurements using Statham pressure transducers Aortic dP/dt was continuously derived by an R C differentiating circuit

A right thoracotomy was performed at the fourth intercostal space the pericardium was incised and a traction snare was placed on the right atrial appendage Complete A V block was produced by injection of formalin into the area of the bundle of His as described by Steiner and Kovalik[20] The right hemithorax was then closed and a left thoracotomy was performed at the fifth intercostal space The pericardium was incised, and a 14 or 16 mm electromagnetic flow transducer (Statham) was placed on the ascending aorta The circumflex branch of the left coronary artery was dissected free of epicardium and connective tissue approximately 1 cm distal to its origin for application of a 2 5 mm electromagnetic flow transducer (Biotronex) Both probes were connected to a Statham sine wave electromagnetic flow meter model M 4000 The circumflex artery was also dissected free approximately 1 cm distal to the flow probe for placement of a variable inflow occlusion clamp[1] A polyethylene tube was inserted directly into the great cardiac vein and was advanced to the middle of the coronary sinus for sampling A pacemaker catheter was sutured to

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the apex of the right ventricle for maintenance of constant rate throughout the experiment Aortic and venous pressures aortic dP/dt, aortic and circumflex coronary artery flows and electrocardiogram Lead II were recorded simultaneously on a Sanborn six channel direct writing recorder

The following calculations were carried out for each time period

Stroke volume = cardiac output/heart rate = ml /beat

Mean systolic ejection rate = M S E R = stroke volume/systolic ejection time = ml / sec

Left ventricular minute work = Kg M /min =

$$\frac{(13\,6 \times \text{mean systolic pressure} \times \text{cardiac output})}{1{,}000}$$

Pressure time/minute = mean systolic pressure × systolic ejection time × heart rate = mm Hg sec /min Results are expressed as mean ± standard error of the mean as calculated by standard methods and the paired t test used to assess the significance of changes in the data

Arterial and coronary sinus pH, PO_2 and PCO_2 were measured frequently using an IL blood gas analyzer Arterial and coronary sinus lactate and pyruvate were measured by enzymatic method as described by Marbach and Weil [22]

The experiment was divided into four time periods Time A represents control measurements The heart was paced at a constant rate of 75 beats per minute In glucagon* studies 10 mg propranolol† was administered ten minutes prior to Time A with an additional 1 mg every ten minutes to insure continued beta adrenergic blockade Circumflex coronary artery flow was then decreased by 50 to 90 per cent, and measurements were repeated after 15 to 20 minutes (Time B) Coronary blood flow was kept constant at this rate throughout the experiment Isoproterenol‡ or glucagon was then administered for 15 to 20 minutes and measurements were repeated (Time C) Isoproterenol was infused at a constant rate of 3 mcg per minute Glucagon was given as a 1 mg bolus followed by constant infusion of 35 mcg per minute The drug was then stopped and measurements were made after 15 minutes (Time D)

* Glucagon = glucagon for injection manufactured by Eli Lilly & Co Inc Indianapolis Ind

† Propranolol = Inderal manufactured by Ayerst Laboratories New York N Y

‡ Isoproterenol = Isuprel manufactured by Winthrop Laboratories New York N Y

Results

Isoproterenol Results of the series of seven animals which received isoproterenol, 3 mcg per kilogram of body weight for 15 minutes are summarized in Table 1 Ventricular fibrillation occurred in four of seven animals shortly before Time D, and values shown represent measurements obtained immediately prior to fibrillation

Reduction of coronary inflow by 50 to 90 per cent produced significant reductions in aortic flow (−25 6 per cent) stroke volume (−19 9 per cent), M S E R (−24 5 per cent) and LV minute work (−26 5 per cent) Mean aortic pressure fell slightly following partial occlusion and fell further with isoproterenol infusion Those animals with highest initial pressures had the greatest fall with isoproterenol whereas those with lower pressures had only negligible changes However these changes were found to be not statistically significant. The calculated pressure time per minute reflected the changes in aortic pressure and were also not significantly altered providing little information regarding any increased oxygen requirement due to isoproterenol

Positive inotropic effects of isoproterenol infusion are evidenced by increases in aortic flow (+88 7 per cent) stroke volume (+22 2 per cent) dP/dt (+71 9 per cent) and M S E R (+50 0 per cent) This positive change in contractile state was associated with a fall in lactate extraction indicative of anaerobiasis

Following discontinuation of isoproterenol infusion, there was a slight but not statistically significant rise in mean aortic pressure There was a decrease in aortic flow stroke volume dP/dt M S E R, and left ventricular minute work These parameters fell to a level below that prior to infusion which may represent myocardial depression due to drug induced anaerobiasis or prolonged anesthesia and manipulations in an open chested animal Ventricular fibrillation occurred in four of seven animals prior to final lactic acid sample collection Two of the remaining animals showed a return to lactate extractions

Table I Effects of isoproterenol infusion in the presence of restricted coronary inflow*

	Control	*p*†	*Occlusion*	*p*	*Infusion*	*p*	*Post infusion*
Heart rate	75		75		75		75
Mean arterial pressure (mm Hg)	80 ± 7.3	ns	73.3 ± 10 4	ns	57.2 ± 7 3	ns	76 ± 9 6
Aortic flow (ml /min)	1 290 ± 251	0 02	960 ± 300	0 01	1 810 ± 420	0 01	825 ± 200
dP/dt (mm Hg/sec)	1 102 ± 193	ns	1 104 ± 207	0 01	1 900 ± 298	0 01	973 ± 142
t peak dP/dt (sec)	0 03 ± 0	ns	0 03 ± 04	ns	0 02 ± 04	ns	0 03 ± 014
Systolic ejection time (sec)	0 20 ± 02	ns	0 20 ± 02	ns	0 19 ± 02	ns	0.20 ± 02
M.S E R (ml /sec)	98 ± 13	0 02	74 ± 13	0 05	111 ± 19	0 01	60 ± 7
Stroke volume (ml)	19 1 ± 3 4	0 05	16 3 ± 3 0	0 05	18 7 ± 3 1	0 01	10 8 ± 1 0
LV minute work (Kg M /min)	2 470 ± 382	0 02	1 814 ± 349	ns	2 343 ± 492	0 05	1 175 ± 184
Pressure time/min (mm Hg sec /min)	1 552 ± 83	ns	1 449 ± 134	ns	1 295 ± 175	ns	1,338 ± 128
% lactate extraction	+31 4 ± 7 9		+21 5 ± 10 0		−18 9 ± 17		4/7 ventricular fibrillation

Results expressed as mean ± standard err r of the me n
†P alues by paired t test, indicate statistical differences.

Table II Effects of glucagon infusion in the presence of restricted coronary inflow*

	Control	*p*†	*Occlusion*	*p*	*Infusion*	*p*	*Post infusion*
Heart rate	75		75		75		75
Mean arterial pressure (mm Hg)	93 3 ± 23	0 01	70 ± 17	ns	66 ± 16	ns	63 ± 11
Aortic flow (ml /min.)	1 555 ± 482	0 01	916 ± 313	0 01	1,200 ± 408	0 01	903 ± 300
dP dt (mm Hg/sec)	1 153 ± 168	0 02	772 ± 120	0 01	1 152 ± 114	0 05	874 ± 45
t peak dP/dt (sec)	0 05 ± 02	ns	0 07 ± 03	ns	0 05 ± 02	ns	0 07 ± 0?
Systolic ejection time (sec)	0 19 ± 02	ns	0 19 ± 03	ns	0 17 ± 02	ns	0 19 ± 0?
M.S E R (ml /sec)	102 ± 19	0 01	60 ± 11	0 01	81 ± 16	0 01	58 ± 12
Stroke volume (ml)	19 ± 7 7	0 05	11 ± 4 9	0 05	14 ± 6 6	0 01	11 ± 5
LV minute work (Kg M./min.)	2 478 ± 356	0 01	1 113 ± 190	0 02	1 521 ± 154	0 01	1 071 ± 148
Pressure time/min (mm Hg sec /min)	1 905 ± 272	0 01	1 441 ± 164	ns	1 381 ± 177	ns	1 369 ± 144
% lactate extraction	+17.3 ± 3 2		+13 8 ± 2 2		−2 0 ± 3 4		+26 ± 6

Results expressed a m an ± standard error of the mean
†P v lues by pai ed t test, ind ate statist cal differences

of 35 per cent and 40 per cent and one main tained a level of −58 per cent

Glucagon Results of the series of seven animals which received glucagon as a bolus of 1 mg followed by infusion of 35 mcg per minute for 15 minutes in the presence of beta drenergic blockade with propranolol are sum marized in Table II

Coronary flow reduction produced significant reductions in aortic flow (−41 2 per cent) stroke volume (−42 1 per cent) dP/dt (−33 2 per cent) M S E R (−41 2 per cent) and left ventricular minute work (−55 0 per cent) There was also a decrease in mean aortic pressure and pressure time per minute but these did not change further during or after glucagon administra tion

Glucagon produced positive inotropism as seen

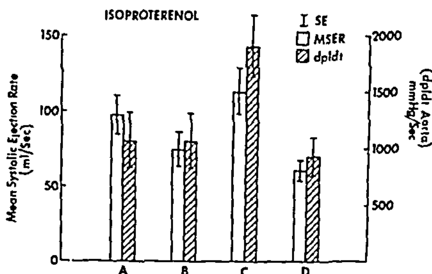


Fig 1 Effect of isoproterenol infusion on mean systolic ejection rate and aortic dP/dt *A* = control *B* = 15 minutes with restricted coronary inflow *C* = 15 minutes of drug infusion *D* = 15 minutes after cessation of drug infusion SE ± standard error of the mean

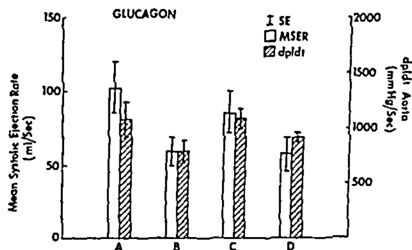


Fig 2 Effect of glucagon infusion on mean systolic ejection rate and aortic dP/dt Abbreviations same as in Fig 1

in a rise in aortic flow (+30 9 per cent) stroke volume (+27 3 per cent) dP/dt (+49 3 per cent) M S E R (+35 0 per cent) and left ventricular minute work (+36 7 per cent) These changes were associated with a fall in lactate extraction to anaerobic levels

Following cessation of glucagon administration, parameters of cardiac output and contractile state returned to levels very similar to preinfusion values

The absence of post infusion depression of myocardial function may reflect some slight variation in experimental technique the less marked fall of lactate extraction or some difference in the effects of the two drugs

Comparison of isoproterenol and glucagon Figs 1 to 5 show comparative effects of isoproterenol and glucagon adminstration in the presence of restricted coronary inflow Both drugs caused directionally similar effects but were somewhat different in magnitude However no effort was made to compare the drugs on a dose effect basis The significant features are that both drugs caused a rise in parameters of inotropism and cardiac work—i e aortic dP/dt M S E R , and left ventricular minute work (Figs 1 2 3) In both cases these changes were accompanied by changes in lactate extraction which demonstrate anaerobic metabolism (Fig 4) Neither isoproterenol nor glucagon caused a significant change in calculated pressure time per minute (Fig 5) despite other evidence of increased heart work and increased oxygen consumption, implying this is a poor index of contractility and oxygen demand

Isoproterenol increased cardiac output and

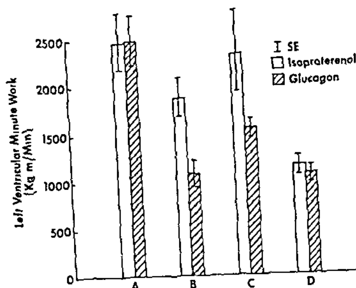


Fig 3 Comparative effects of isoproterenol and glucagon infusion on left ventricular minute work. Abbreviations same as in Fig 1

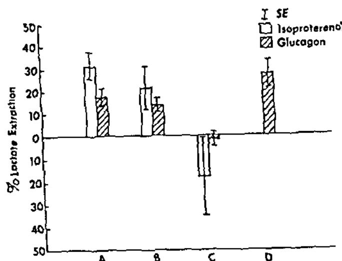


Fig 4 Comparative effects of isoproterenol and glucagon infusion on myocardial lactate extraction. Abbreviations same as Fig 1

inotropism in the presence of regional decreased coronary inflow but at the expense of increased oxygen demand and a shift from aerobic metabolism to net lactate production Also there was a fall in arterial pressure and diminished coronary perfusion pressure combined with enhanced inotropic state may account for the high mortality rate due to isoproterenol encountered in this series of animals.

Glucagon on the other hand, produced the myocardial anaerobiasis by its inotropic effect alone without alteration of perfusion pressure heart rate or apparent volume change Thus the actions of these drugs are associated with increasing myocardial hypoxia in the presence of regional restriction of coronary inflow

Discussion

Both isoproterenol and glucagon have been used extensively for the hypotension and congestive failure associated with myocardial infarction

Cardiac effects of isoproterenol in both normal and abnormal hearts include marked inotropic and chronotropic effects [1,2,6] These are associated with an increased O_2 consumption [7] In the pa

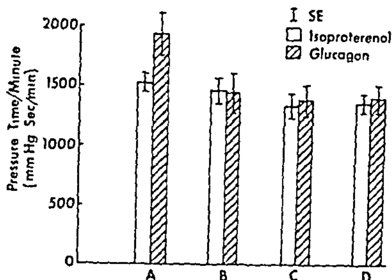


Fig 5 Comparative effects of isoproterenol and glucagon infusion on calculated pressure time per minute Abbreviations same as in Fig 1

tient with obstructive disease of the coronaries the use of isoproterenol has been associated with the development of ischemic ST segment changes[23] and myocardial lactate production [8,9] Part of the increased energy requirement induced by isoproterenol may be offset by a reduction in ventricular dimensions [6] However if there is no improvement in the determinants of myocardial oxygen consumption a reduction in heart rate or ventricular wall tension and further deterioration of myocardial performance would be expected This is supported by the finding of 57 per cent mortality rate (4 of 7) in this series of animals despite an improvement in cardiac output Similar deleterious effects of isoproterenol have been described by others [4,5,10,24,26]

In contrast, glucagon has been used with variable success in low cardiac output states The effects in normal hearts include a positive inotropic and moderate chronotropic effects, manifested by an increased cardiac output, dP/dt, and heart rate Also augmented atrioventricular conduction and reduction of systemic vascular resistance have been demonstrated These effects occur in the absence of catecholamines, in the presence of beta adrenergic blockade or full digitalization [13,14,17,1 27,28] It has been noted to be less effective in congestive heart failure, presumably because of the inability to activate adenyl cyclase [29] Since glucagon's effect does not depend on beta adrenergic receptors, conceivably different metabolic effects might be expected Diamond and colleagues[12] suggested that glucagon offered theoretical advantages since it produced the same increases in cardiac output for a smaller increase in tension time index, a major determinant of myocardial oxygen consumption The use of tension time index and pressure time per minute however ignores the rate of pressure development as a major index of oxygen demand [30] In the present series, there was no significant change in the calculated pressure time per minute in spite of a marked increase in mean systolic ejection rate following the use of glucagon An increase in myocardial oxygen consumption in man and normal animals has been noted following glucagon administration [31]

No net change in myocardial oxygen consumption was noted following glucagon administration in conscious dogs with myocardial infarction [32] It was postulated that the decrease in energy requirement incident to the reduction in wall tension counterbalanced the expected increase in oxygen requirements due to the glucagon induced inotropy The degree of oxygen requirement following glucagon has been related to the magnitude of the left ventricular end diastolic pressure (LVEDP) [33] Initial LVEDP below 15 cm H_2O was associated with a significant increase in myocardial oxygen consumption whereas a decrease or no change in oxygen consumption was found when the initial LVEDP was elevated above 15 cm H_2O and fell substantially The fall was associated with a greater reduction in ventricular dimensions The present study indicates a marked sustained shift to

anaerobic glycolysis caused by glucagon in the presence of restricted coronary inflow and a prompt return toward normal lactate extraction following cessation of glucagon infusion in spite of continued restriction of coronary blood flow of the same magnitude The only hemodynamic changes following glucagon were those reflecting increased inotropy specifically M S E R and rate of pressure development It is likely that there was not a commensurate fall in ventricular myocardial tension to offset the increased oxygen requirement of glucagon induced inotropy Such a situation might be expected in human coronary disease with fixed coronary inflow

The hemodynamic and metabolic changes of isoproterenol and glucagon are directionally similar in spite of different pharmacologic receptor sites The different magnitude of response may be dose related but no effort was made to compare the two drugs on a dose response basis However in both instances the improvement in cardiac performance is associated with an increasing myocardial oxygen consumption as evidenced by decreased lactate extraction In the presence of restricted coronary inflow this increased anaerobiasis may be the limiting factor in survival

Summary

Anesthetized mongrel dogs were paced at constant heart rates after creation of complete A V block by formalin injection The circumflex artery was narrowed by 50 to 90 per cent using a variable occlusion clamp Arterial and coronary sinus pH Po_2 Pco_2 lactate and pyruvate levels aortic and right atrial pressures aortic and circumflex artery flows aortic dP/dt and electrocardiogram Lead II were monitored Recordings were made before and after circumflex narrowing during and after isoproterenol infusion 3 mcg per minute (7 animals) or during and after glucagon infusion 35 mcg per minute (7 animals pre blocked with propranolol) Isoproterenol caused positive inotropic changes associated with a marked decrease in myocardial lactate extraction (−37 4 per cent) and a decrease in mean aortic pressure Glucagon infusion caused similar changes of increased inotropy and a decrease in lactate extraction however there was no significant change in aortic pressure

It is concluded that in the presence of restricted coronary arterial inflow use of the potent inotropic agents isoproterenol and glucagon may result in progressive deterioration due to excessive energy utilization induced by these agents

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The correlation of metabolic and ultrastructural changes in emetine myocardial toxicity

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Clinical studies have documented the cardiac toxicity of emetine when used therapeutically [1] and use of this drug is now restricted to the complicated case of amebiasis usually in the event of liver abscess Emetine has been reported to alter cellular metabolism by its effects on carbohydrate metabolism [2] protein synthesis [3] and oxidative phosphorylation [4-8] We have recently had an opportunity to study serial ultrastructural changes in the myocardium of dogs treated with emetine in a dose comparable to that used in man [9] Selective mitochondrial damage was noted. In the present study mitochondrial preparations were studied to detect emetine effect on oxidative phosphorylation using parameters not previously reported in an effort to correlate metabolic change with specific ultrastructural abnormalities

Method

Dogs were given intravenous pentobarbital (30 mg per kilogram of body weight) and a thoracotomy was performed with rapid extirpation of the heart. Approximately 7 Gm of apical myocardium was taken to the processing room which was maintained at 0 to 4° C The tissue was washed with homogenizing solution * minced, and homogenized by methods similar to those previously outlined.[10] Mitochondria was separated and suspended in a medium containing 0 25 M sucrose 001 M neutralized EDTA 0 01 M tris pH 7 4 7 5 mm potassium phosphate pH 7 4 and 0 01 M substrate in a final volume of 3 ml. Substrates were neutral sodium salts of L glutamic acid (0 01 M) or pyruvic acid (0 01 M) plus L-malic acid (0 005 M) the latter combination being referred to as malate In each experiment normal mitochondria was tested simultaneously with mitochondria treated with emetine at three different concentrations at 25° C Emetine hydrochloride U S P * in pure crystalline form was weighed accurately dilute molar solutions prepared, and 0 1 ml aliquots were added to the cuvette to obtain the desired concentrations

Oxidative phosphorylation studies were done by the polarographic method[11] and were completed within 90 minutes following sacrifice of the animals Indices obtained were mitochondrial oxygen consumption (μatoms of oxygen consumed per milligram of mitrochondrial protein per minute) ADP O ratio (μmoles of adenosine diphosphate (ADP) phosphorylated per μatoms of oxygen consumed) and respiratory control ratio (the ratio of oxygen consumption in the presence of ADP compared to that after ADP has been utilized)

Mitochondrial protein was determined by a standard method.[12] Attempts were made to consistently achieve 2 mg /ml mitrochondrial protein ADP assays were determined spectrophotometrically [13]

Results

Oxygen consumption of the emetine treated mitochondria proceeded at the same rate as the

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* 0 5 M sucrose 0 001 M EDTA nd 0 01 T is bu r

* City Chemical Corp 13 West 22nd St., New York, N Y

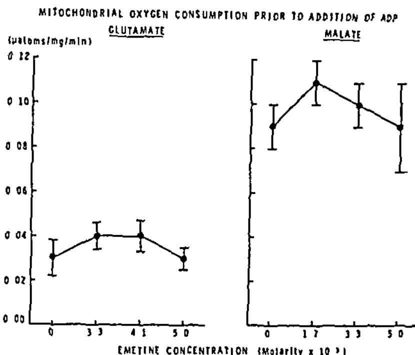


Fig 1 The oxygen consumption of normal and emetine treated mitochondria prior to the addition of ADP is shown here plotted as µatoms of oxygen consumed per milligram of mitochondrial protein per minute Means and standard deviations are shown There is no significant difference between normal and emetine treated mitochondria in either glutamate or malate substrate

normal mitochondrial preparation prior to the addition of ADP This data is presented in Fig 1 There is no significant difference between the normal mitochondria and emetine treated mitochondria

The effects of emetine on the oxygen consumption, respiratory control index, and ADP O ratio in glutamate and malate substrates after addition of ADP are outlined in Fig 2

The results show that emetine acts to inhibit oxidative phosphorylation this is related to concentration and occurs with both substrates The most striking change occurs in the respiratory control index and is due to the slow rate of oxygen consumption during State 4 of respiration This is in contrast to what one would expect if uncoupling was the predominant mode of action, since oxygen consumption would have been increased in State 4

Discussion

Our experimental results establish emetine as an inhibitor and not an uncoupler of oxidative phosphorylation In this action it is very similar to oligomycin [14] an agent considered to be an inhibitor of oxidative phosphorylation Oligomycin has been used to study metabolic reaction sequences[15] and it is entirely possible that emetine could also prove useful in this regard It is of interest that both agents are antibiotics in the broad sense

Oxidative phosphorylation occurs within the mitochondria and it is the organelle specifically affected by emetine as we have previously demonstrated[9] Therefore, there is a correlation between the anatomical site of action and a measureable metabolic derangement of the structure No such observations have been reported for oligomycin

The mechanism of the change in the electrocardiogram in man[16] and in the experimental animal[17] after emetine administration is unknown Non specific T wave changes and conduction abnormalities are frequent manifestations of emetine myocarditis The role of altered mitochondria function in these observations remains to be elucidated

Further studies may reveal a more specific metabolic effect of emetine as an inhibitor of oxidative phosphorylation Continued caution is necessary in the use of this cardiotoxic agent

Summary

Emetine exerts a specific effect on mitochondrial function and structure Its action is to inhibit oxidative phosphorylation as measured by

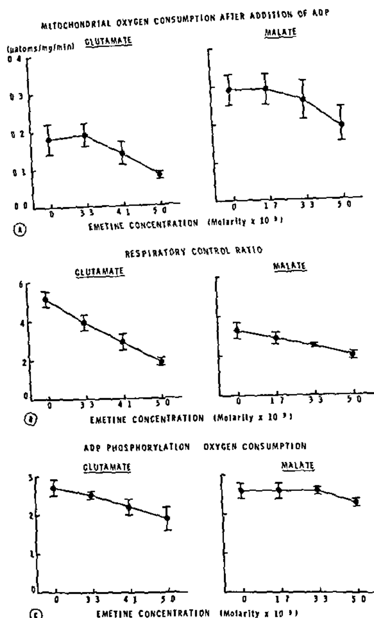


Fig 2 **A B and C** Emetine inhibits oxidative phosphorylation of heart mitochondria after the addition of ADP as reflected by these findings showing means and standard deviations of the following indices *A* Oxygen con sumption of normal and emetine treated mitochondria (µatoms of oxygen consumed per milligram of mito chondrial protein per minute) *B* Respiratory control ratio (the ratio of oxygen consumption in the presence of ADP compared to that after ADP has been utilized) *C* ADP oxygen ratio (µmoles of adenosine diphosphate phosphorylated per µatoms of oxygen consumed)

mitochondrial oxygen consumption ADP O ratio and the respiratory control ratio Our ob servations correlate documented specific struc tural abnormality with a metabolic change These results probably account for some of the cardiotoxicity known to result from administra tion of emetine

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Case reports

Congenital diverticulum of the left ventricle

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Congenital diverticulum of the muscular portion of the left ventricle has been reported in only 29 patients but it is a potentially lethal anomaly as sudden rupture and death is reported in over half of the cases[1-4] This anomaly is usually associated with defects in midline structures such as omphalocele and diaphragmatic hernia[2] This report describes the identification and successful surgical removal of a left ventricular diverticulum in a child with defects in other midline structures including pyloric stenosis a previously undescribed associated anomaly

Case report

A D R a 3 year old boy presented to the Department of Pediatric Cardiology Texas Children s Hospital because of a pulsatile epigastric mass At birth in another hospital the patient was noted to have an omphalocele which was repaired primarily During the operation a pulsatile structure was noted in the epigastrum but was not disturbed At age 6 weeks, because of persistent vomiting the patient underwent successful correction of pyloric stenosis The pulsatile mass was again noted. The child did well following this procedure but over the succeeding 3 years the patient s family noted increasing prominence of the pulsatile epigastric mass and brought the child for evaluation

Physical examination revealed a well developed, well nourished Caucasian boy in no distress Weight was 28 pounds height 38 inches Blood pressure was 95/60 in the upper extremities and 100/60 in the lower extremities The sternum was short with a mass pulsating in synchrony with the cardiac apex at the fifth left intercostal space extending from the inferior margin of the sternum to the area of the scar of omphalo ele repair The mass was tubular and it was possible to palpate its complete circumference near the caudal end. Auscultation revealed a Grade I/VI low pitched early systolic murmur at the lower left sternal border An electrocardiogram (Fig 1 *A*) demonstrated a terminal conduction delay pattern. A vectrocardiogram (Fig 2 *A*) showed terminal slowing which was directed to the right and posteriorly An ape xcardiogram (Fig 3) showed that the initial excursion of the apex at the fifth left intercostal space was simultaneous with the initial excursion at the tip of the epigastric mass

Cardiac catheterization and angiography was performed. A left ventricular angiogram (Fig 4) showed the mass to be synchronously contractile end in direct continuity with the left ventricle The tip of the diverticulum and its opening into the body of the left ventricular cavity contracted simultaneously No obstruction at the opening of the diverticulum was noted at any time during the cardiac cycle An attempt to place a catheter into the diverticulum was unsuccessful because of multiple premature contractions when this maneuver was tried. No other associated cardiac defects were found.

Successful surgical removal of the diverticulum was performed by Dr D A Cooley using a transabdominal approach without cardiopulmonary bypass The diaphragmatic hernia through which the structure penetrated into the abdominal cavity was also repaired. The diverticulum was covered by pericardium which communicated directly with the intrathoracic pericardial space Postoperatively the conduction delay disappeared on the electrocardiogram (Fig 1 *B*) and the vectrocardiogram (Fig 2 *B*) Normal precordial movements were recorded on the apexcardiogram

Discussion

Congenital diverticulum of the left ventricle was first documented in 1866 but fewer than 30 cases have since been reported.[1-4] Cantrell and

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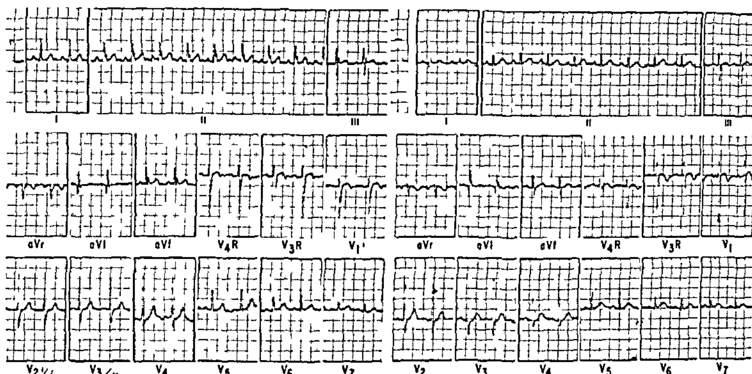


Fig 1A Preoperative electrocardiogram demonstrating a conduction delay pattern most prominent in the inferior leads

Fig 1B Normal postoperative electrocardiogram

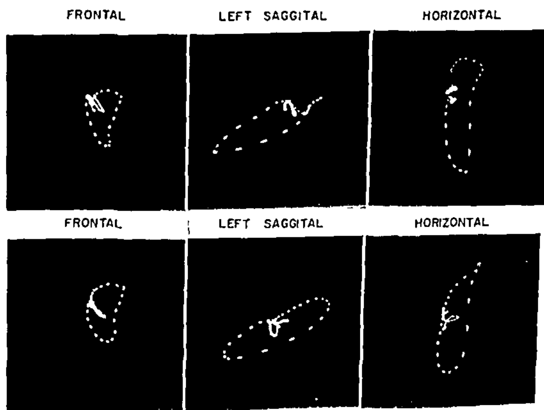


Fig 2 *Upper panel*, Preoperative vectorcardiogram showing the terminal conduction delay directed to the right and posteriorly (All projections are done with the Frank system dash interval of 2 5 msec 0 5 mv/cm with the large portion of the dash forward) *Lower panel*, Normal postoperative vectorcardiogram

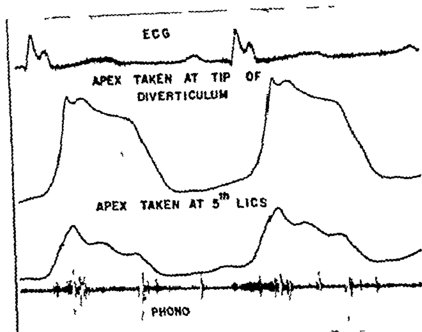


Fig 3. Preoperative apexcardiogram demonstrating simultaneous initial systolic movement of the apex taken at the tip of the diverticulum as well as at the fifth left intercostal space

colleagues[2] have proposed that muscular diverticuli are part of a syndrome of congenital defects that may include malrotation of the heart with mesocardia or dextrorotation associated intracardiac anomalies a deficient lower sternum a diaphragmatic defect, and midline abdominal muscular abnormalities such as omphalocele umbilical hernia and diastatis recti. Pyloric stenosis has not been previously described as part of this syndrome Edgett and associates[3] have suggested that left ventricular diverticuli be divided into groups—the muscular type as presented here and the fibrous type which are not associated with midline defects usually communicate with the left ventricle near the mitral annulus, and usually occur in Negroes Diverticuli of the right ventricle are rarer than those of the left ventricle [4,5]

Electrocardiograms in patients with muscular diverticuli have been noted to be either normal or to manifest intraventricular conduction delays Lowe and colleagues[6] showed in their patient that the wave of depolarization was delayed in reaching the diverticulum. This could theoretically result in an out of phase contraction between the body of the left ventricle and the diverticulum, with partial occlusion at the neck of the diverticulum This has been proposed as a major contributing force in the rupture of the diverticuli which has been seen in over half of the reported cases most frequently in early infancy [8] The apexcardiogram in the present case as well as the angiocardiogram suggests that this phenomenon did not occur although the cavity of the diverticulum was not catheterized for pressure measurement.

The terminal conduction delay seen on the preoperative scalar electrocardiogram and confirmed by the vectorcardiogram was abolished after surgical removal of the diverticulum It might be postulated that the Purkinje system directly innervated the diverticulum so that its contractions were in synchrony with the rest of the left ventricle Alternatively the ostium of the diverticulum was of sufficient size that a synchronous contraction did not occlude it

Summary

The clinical and hemodynamic features in a three year old boy with a congenital muscular diverticulum of the left ventricle associated with omphalocele diaphragmatic hernia and pyloric stenosis are presented. Preoperative angiocardiograms showed no obstruction to outflow from the diverticulum, the mechanism previously postulated as contributing to the spontaneous rupture and death reported in over half of the patients with this lesion An intraventricular



Fig 4A Systolic frame of the left ventricular angiogram showing contraction of the diverticulum without narrowing of the opening of the diverticulum into the left ventricle

Fig 4B Diastolic frame illustrating the full extent of the diverticulum and its relationship to the chest and abdominal walls

conduction delay noted on preoperative electrocardiograms disappeared after successful surgical removal of the diverticulum

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Intrapericardial left atrial aneurysm

Report of a Case and a Review of the Literature

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In 1938 Semans and Taussig[1] published a case of intrapericardial left atrial aneurysm. Thirteen cases[2-14] verified at autopsy or operation have been reported during the last twenty years. Left atrial aneurysm may cause severe tachyarrhythmias, systemic embolism, and heart failure. As it is curable by operation, we find it justified to report one further case and give a review of the literature.

Case report

A 38-year-old male was admitted in May, 1970, because of atrial fibrillation and suspicion of congenital heart disease. There was no family history of heart disease. Apart from the present disease the patient had been healthy. At age 17 he was told after x-ray mass screening that he had an enlarged heart, and congenital heart disease was suggested. For that reason he was not accepted for military service. Attacks of palpitation and slight dyspnea were experienced by the patient for the first time at the age of 35. The attacks were of one to two hours' duration and often provoked by moderate exercise. An electrocardiogram from such an episode revealed supraventricular tachycardia with a ventricular rate of 150 per minute. Treatment with digitalis was started at the local hospital. The attacks almost disappeared for the following three years. At reappearance the patient was admitted to University Hospital, Medical Department B. Physical examination was completely normal apart from an irregular pulse. The electrocardiogram showed only atrial fibrillation.

The roentgenogram of the chest (Fig. 1) showed an increased heart volume, 580 ml. per M^2 BS, with a slight prominence along the left heart border just apical to the pulmonary segment. DC conversion of the atrial fibrillation to sinus rhythm was successfully performed and the patient was discharged to continued treatment with digitalis. Six months later the attacks of palpitation and dyspnea reappeared. During one such attack the electrocardiogram showed sinus tachycardia with a 2:1 block and a ventricular rate of 120 per minute. After six months the patient was readmitted with atrial fibrillation for angiocardiographic and hemodynamic investigations. The electrocardiogram showed intermittent atrial fibrillation and sinus rhythm. At a right heart catheterization performed when the patient had sinus rhythm, normal pressures were found in the right side and in the pulmonary wedge position. The cardiac index was 2.3 L. per minute per M^2 BS. Pulmonary angiocardiography showed a contrast-filled non-pulsating dilatation in the left side of the heart which suggested a Valsalva aneurysm; however, aortography was normal. A transseptal catheterization was then performed: ventriculography showed a normal left ventricle. Finally a contrast injection in the left atrium revealed a nonpulsating dilation of the left atrial appendage (Fig. 2) from which the contrast medium cleared very slowly. Operation revealed an 8 by 7 by 7 cm. intrapericardial aneurysm of the left atrial appendage. The aneurysm communicated with the left atrium via a neck 2.5 cm. in diameter at the posterior aspect of the aneurysm. At the start of the operation atrial fibrillation was seen. Spontaneous sinus rhythm appeared after clamping the neck. No thrombi were found in the aneurysm or in the left atrium and the mitral valve felt normal. Microscopic sections of the aneurysm wall showed hypertrophy of the myocardial fibers and mild lymphocytic infiltration around the vessels.

The patient made an uneventful recovery. He was seen as an outpatient six months later without complaints, showing sinus rhythm and a nearly normal chest x-ray.

Discussion

Intrapericardial left atrial aneurysm is a rare abnormality. We have found reports of 14 cases[1-14] in the literature. Two cases[1,2] were verified at autopsy and 13 cases[3-14] including our own were found at operation. These 15 cases form the basis for the following review.

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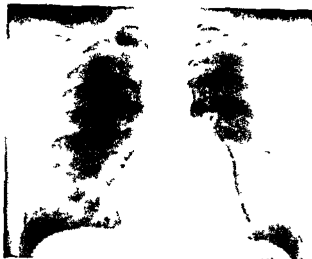


Fig 1 Chest x ray frontal view showing bulging of the left heart border suggestive of an enlargement of the left atrium

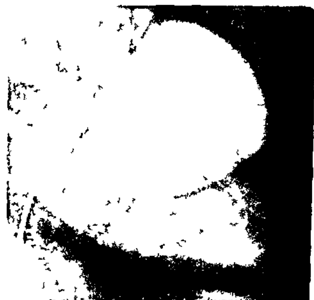


Fig 2 Trans septal left atrial angiocardiogram showing large dilatation of the left atrial appendage The left atrium and ventricle are of normal size

Four cases [4 15 17] which according to angiocardiographic studies probably have this anomaly are not included because the condition of the pericardium was not stated

Age and sex The 15 cases include nine males *and six females Five patients were less than 10* years old, 7 between 10 and 40 years and 3 over 40 years of age at the time of diagnosis The youngest was 5 months [12] the oldest 64 years [2] Onset of symptoms varied greatly In one patient,[12] symptoms started immediately after birth in another case at age 42 [9]

Symptoms *Palpitations* with slight dyspnea constant or paroxysmal, was described in 11 patients and was the only complaint in six patients Cerebral embolism was reported in 4 patients [2 3 6 14] One of these[4] also had several emboli *in the femoral artery* Three of the patients had more than one embolic episode The disease started with a cerebral *embolus* in three patients and was the only complaint in two patients Precordial pain without relation to exercise was reported as the only symptom in one patient [10] One patient[11] *on five occasions received* an intraoral injection of local anesthetic containing norepinephrine and developed the abrupt onset of rapid, regular palpitations with retrosternal pain, *shortness of breath* and presyncopal feelings Severe right and left heart failure was seen in one patient[1] with an enor*mous aneurysm of the left atrium This patient* died two days after admission in severe congestive heart failure In one patient[7] attacks of abdominal pain and fainting were described These symptoms persisted after successful removal of the aneurysm It is questionable whether they were related to the aneurysm *Stethoscopy of the heart* was normal in eight patients including our own case A *faint systolic* murmur (*Grade 1 3 of* 6) was heard along the left sternal border in 3 patients and at the apex in 2 patients [10 11] In one patient,[4] who had also an atrial septal defect (ASD) *a persistently split second sound* and a systolic ejection murmur over the pulmonary area were described The patient reported by Semans and Taussig[1] was in severe congestive *heart failure and had systolic and diastolic* murmurs at the apex and gallop rhythm *The electrocardiogram* was normal in four patients and was normal in six patients [2 5 6 9 11] including our own case except for episodes of atrial fibrillation or regular supraventricular tachycardia Three patients[3 12 13] had atrial fibrillation and one[1] a *persistent supraventricu*lar tachycardia One patient[4] showed changes compatible with an atrial septal defect of secundum type

Roentgenogram of the chest *In nine patients* the plain chest x ray showed a mass protruding anteriorly and to the left between the pulmo*nary artery and the left ventricle* In five patients a marked dilatation of the heart without definite chamber enlargement was seen Three of these patients[1 3 13] *had very large aneurysms* one[12] multiple aneurysms of the right and left atrium and one[4] an ASD too In one patient[7] a rounded mass is described *in the posterior*

mediastinum posterior and inferior to the right hilum of the lung

Angiocardiography with contrast injection in the right atrium (two patients), pulmonary artery (three patients) and the left atrium (three patients) confirmed the diagnosis in all cases but one the patient with ASD in whom an angiocardiogram from the right atrium gave only suspicion of left atrium aneurysm but not a definite diagnosis

Associated anomalies One patient[4] had a secundum ASD and one[12] a pedunculated hamartoma of the liver

Operation was carried out in 13 patients The aneurysm was removed without difficulties with an uneventful postoperative course in 10 patients In the patient[12] with multiple aneurysms of the right and left atrium the operation was performed without difficulties but postoperatively the patient got a small cerebral embolus and atrial tachycardia persisted for a few days In two patients the aneurysm was not removed at the first operation One patient[4] with ASD developed a supraventricular tachycardia at the operation and it was decided to reoperate later The seventh day postoperatively atrial flutter developed and from the ninth day postoperatively several arterial thromboembolic episodes occurred. After three weeks the patient was reoperated and 2 organized thrombi were found in the aneurysm In the second patient[6] an explorative thoracotomy was performed at age 27 the pericardium was opened but the aneurysm was not resected Twenty months later the patient suffered sudden loss of vision of the left eye with episodes of paresthesias of the left arm probably due to a cerebral embolus The patient was reoperated and the aneurysm was removed At this operation thrombi were found in the aneurysm.

Thrombi in the aneurysm were found in five patients[3,8,9] at operation Three of these patients[3,4,6] had thromboembolic episodes shortly before the operation One patient[14] was on continous anticoagulant treatment for four years because of several systemic emboli and had no thrombi in the aneurysm

After the operation all patients got sinus rhythm either spontaneously or after a small dosage of quinidine

Two patients died without operation one[1] from congestive heart failure and one[2] from breast carcinoma The latter patient had a history of several thromboembolic episodes and organized thrombi in the aneurysm

Pathoanatomy Four different types of aneurysm have been described. In seven patients the aneurysm apparently originated from the left atrial appendage In four patients[1,2,3,9] a normal appendage was seen on the top of the aneurysm In one patient[7] the aneurysm was situated inferiorly to the inferior right pulmonary vein and another patient[11] had multiple aneurysms, five on the right and two on the left atrial appendage

The aneurysm usually was thin walled Histopathological examinations showed the normal atrial wall elements but often few sometimes hypertrophic muscular cells and infiltration with mononuclear cells

Diagnosis From the chest x ray a number of diagnoses may be suggested—e g tumors from other mediastinal structures pericardial cysts and protrusion of the left atrium through a pericardial defect An extracardiac mass must be excluded, and apart from angiocardiography with contrast injection in the pulmonary artery or the left atrium which was diagnostic in all cases Godwin and colleagues[11] found a precordial scan with ^{131}I labeled albumin useful as it may provide evidence that the mass is blood filled

Protrusion of the left atrial appendage through a small pericardial defect may show similar appearance on plain x ray of the chest and angiocardiography may show a slight dilatation of the left atrial appendage [15] Pernot and coworkers[16] have recently made a review of 24 patients with a left sided pericardial defect without congenital cardiovascular abnormalities Thirteen of these patients were without symptoms eight had attacks of precordial pains which could radiate to the left arm and be associated with dyspnea two had attacks of palpitation and dyspnea three had syncopes and one attacks of coughing and small hemoptysis The electrocardiogram was normal in all cases Eleven patients had a faint systolic murmur at the left sternal border None of the patients had thromboembolic complications In six of the 24 cases a left sided diagnostic pneumothorax was carried out and in all cases showed communication between the pleural and the pericardial cavity

Treatment Resection of the aneurysm has

been successful in the reported cases The supraventricular tachyarrhythmias vanished in all instances even in a patient who had atrial fibrillation for 18 years[13] For these reasons and because these patients carry an increased risk of systemic emboli, the aneurysm should be resected

Summary

A case of intrapericardial left atrial aneurysm successfully removed and presenting clinically with intermittent atrial fibrillation is described Fourteen other cases are reported in the literature The first symptom is either palpitation an arterial embolus or precordial pain The diagnosis is confirmed by angiocardiography The aneurysm should be removed

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Electrocardiographic findings in the aged

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The population over age 70 continues to increase and the physician frequently is confronted with the task of evaluating the cardiac status of the elderly patient What tends to complicate the problem is that frequently these patients are either unable to provide accurate histories or have concomitant diseases of other organ systems which exhibit symptom complexes overlapping those usually attributed to cardiovascular disease Therefore the reliability of an objective measurement such as the electrocardiogram (ECG) assumes a greater role in the evaluation of the cardiac status in this group of individuals Often however an abnormal ECG is recorded in patients who have only equivocal or no clinical or other laboratory evidence of heart disease and consequently evaluation of the significance of ECG abnormalities becomes important

Since 1931 a number of studies have been published which have attempted to define the geriatric ECG Earlier literature suggested that changes in conduction voltage and electrical axis could be expected in the aged as the result of the normal aging process [1] It has also been suggested that age related electrocardiographic changes may at least in the United States be due to coronary artery disease [2]

Histochemical and ultrastructural studies of the insect heart reveal that characteristic changes independent of vascular changes do indeed occur with age [3] However further discussion of senile cardiomyopathy is beyond the scope of this paper and has been reviewed in detail elsewhere [3,4] Suffice it to say that a definite relationship between ECG and histologic changes has yet to be established. There are several reports in the literature describing age related shifts in the electrical axis and changes in the QRS voltages with age [5-7] Slight but significant increases were found in P wave duration as well as P R and QRS intervals in males when compared to females of similar age [8,9] While these are of value in epidemiologic studies such changes are too subtle and are affected by a number of variables such as weight configuration of the thorax and body position to be applicable without reservation in clinical evaluation of an individual patient Moreover it has been recently demonstrated that such changes may be within the limits of error of interpretation especially when such measurements are made from a routine direct writing ECG taken at 25 mm per second [10] For these reasons such minor changes are of questionable value particularly as an isolated finding in a single ECG

The purpose of this communication is to review the literature dealing with the ECG in the aged and to present data based on a study of 671 individuals over the age of 65 More specifically the present study will attempt to determine (1) whether the normal ECG in the aged differs from that of the young age groups and (2) whether an abnormal electrocardiogram in the elderly is a reliable index of clinical heart disease

Material and method

The clinical material for this study was selected from two sources Three hundred forty

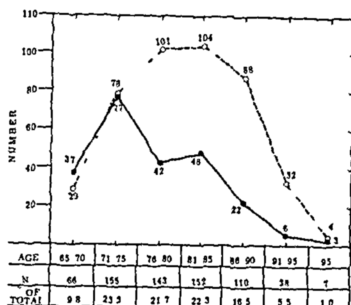
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AGE	65 70	71 75	76 80	81 85	86 90	91 95	95
N	66	155	143	152	110	38	7
OF TOTAL	9 8	23 3	21 7	22 3	16 5	5 5	1 0

Fig 1 Distribution of our 671 subjects according to age and sex (Males are represented by solid circles and solid lines females by open circles and broken lines)

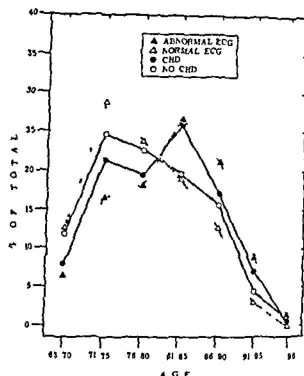


Fig 2 Age distribution of 671 subjects grouped according to the presence or absence of clinical heart disease (*CHD*) and *normal or abnormal ECG is shown above Note the sim*ilarity in the distribution of subjects with abnormal ECG and CHD See text for discussion

one residents of the Indiana Masonic Home comprised one group The remaining 330 cases were selected from a similar population reported previously[11] Both groups consisted of non hospitalized subjects or elderly patients hospitalized for non cardiac disease A history and physical examination with emphasis on the cardiovascular system was performed by one of the authors Because of the advanced age of the subjects the history was frequently not reliable and thus the diagnosis of clinically normal heart may not always be accurate, especially in the presence of angina A standard 12 lead ECG taken at the time of the examination and each individual s medical records including medications and chest roentgenograms were reviewed

The information was recorded on a standard questionnaire A total of 10 clinical variables, 16 drugs and 72 ECG parameters were analyzed Statistical analysis using the Chi square method was performed on each correlation Individual cases in which particular information was not available were excluded and the Chi square was calculated on basis of the remaining number of patients (i e all 671 patients were not used in each comparison) In order to assure as much uniformity as possible from patient to patient all 671 cases were evaluated clinically by one individual Each ECG was reviewed by both authors

Clinical criteria for the diagnosis of heart disease included one or more of the following (1) a history of classical angina pectoris or myocardial infarction (2) congestive heart failure on physical examination (3) cardiomegaly on physical examination and/or x ray and (4) diastolic blood pressure greater than 110 mm Hg

For reasons outlined earlier only unequivocal and clearly defined axis and pattern changes and arrhythmias were included in the abnormal ECG group The ECG was considered abnormal if ST T changes were present in leads other than Leads III and V_1 Normal axis deviation was considered to be between -30 and $+120$ degrees Sinus arrhythmias sinus bradycardia, and tachycardia, less than 6 premature ventricular systoles (PVS), and less than 6 atrial premature systoles (APS) per 12 lead ECG were included in the normal group The PR was considered abnormal if it exceeded 22 second and the QRS when it equalled or exceeded 11 second

Over 100 separate correlations were performed between clinical and ECG variables but only those with sufficient distribution to allow statistical analysis will be presented

Results

Fig 1 represents the age and sex distribution of the population studied According to the cri

teria described above 331 individuals (49 per cent) were found to have clinical evidence of heart disease and in 306 (45 per cent) the ECG was abnormal Table I summarizes the clinical findings in patients with heart disease The criteria for hypertension is admittedly conservative but the elevation of diastolic blood pressure was frequently accompanied by other criteria of heart disease Fig 2 illustrates age distribution of four major groups (1) those with no heart disease (2) those with heart disease (3) those with normal ECG and (4) those with abnormal ECG When the distribution of all four groups is compared with age a bimodal pattern becomes evident The curves representing the incidence of subjects without heart disease and those with normal ECG are similar with a peak incidence at age 71 to 75 On the other hand, the group with clinical evidence of heart disease and the group with abnormal ECG also parallel each other with the peak incidence in the 81 to 85 year age range The above distribution of the normal and abnormal ECG among patients with and without heart disease suggests that the clearly abnormal ECG (as defined earlier) may prove to be a reliable index of heart disease Fifty six per cent of patients with clinical heart disease (CHD) had an abnormal ECG as opposed to 37 per cent of the clinically normal subjects (P < 0001)

Further correlations were performed in search of any particular ECG change which might be more common for a given age or more indications of heart disease Table II summarizes the findings The most frequent abnormality encountered were non specific ST T wave changes recorded in 106 subjects 65 of whom had CHD There was a significant correlation between the ST T change and heart disease at the one per cent level There was no significant increase in frequency with age but a strong correlation with digitalis was noted. Forty two per cent of patients on digitalis had ST T wave changes as opposed to 13 per cent of those not taking the drug (P < 0001) not an unexpected finding When subjects taking digitalis were excluded from the comparison the relationship between ST T wave changes and CHD became insignificant. However the significance of isolated ST changes is difficult to evaluate in a study such as this because of the fact that many of the patients were receiving digitalis.

Table I Clinical findings in 331 subjects with heart disease

Manifestation	*Number of patients*	%
Cardiomegaly	195	59
Congestive heart failure	91	28
Angina pectoris	45	14
Diastolic pressure ≥ 110 mm. Hg	30	9

Left anterior hemiblock was the second most frequent abnormality occurring in 11 per cent It was twice as common in subjects with heart disease but the relationship fell just short of statistical significance However there was a significant increase in frequency with age (P < 005) No examples of left posterior hemiblock were found. Left anterior hemiblock was sometimes associated with right bundle branch block and first degree A V block but insufficient numbers precluded statistical analysis of these subgroups Likewise the six cases suggestive of trifascicular block noted were too few to correlate with other factors

First degree A V block (1 AVB) occurred in 67 subjects There was no significant correlation with heart disease Four of the five cases in which 1°AVB was associated with left bundle branch block (LBBB) had CHD Incidence of 1 AVB did show a significant increase with age (P < 001) This contrasts with the duration of the normal P R interval which showed no statistically significant increase with age These results are summarized in Table III There was no correlation of the duration of the P R interval with sex, digitalis or other medications

Right bundle branch block (RBBB) pattern was seen in 7 1 per cent of our patients and was not statistically related to any other variable examined There was an equal distribution between normals and those with heart disease When plotted against age the distribution was bell shaped, peak frequencies occurring in the 75 to 85 year age range When the 33 cases of LBBB were segregated according to age a similar pattern of distribution was found, peaking somewhat later in the 80 to 90 year group A Chi square value of borderline significance was obtained on these relationships (P < 025)

Table II Correlation of electrocardiographic findings with clinical heart disease*

%	No	ECG abnormality	Clinical evidence of heart disease		P
			Yes	No	
0 9	6	RAD (± +120)†	2	4	—
11 0	74	Total LAHB	50	24	N.S
7 6	51	LAHB only	34	27	N.S
0 5	4	RBBB + LAHB	4	0	—
1 9	13	1 AVB + LAHB	8	5	—
0 9	6	Tri fascicular block	4	2	—
10 0	67	Total 1 AVB (P — R > 0 21 sec)	37	30	N.S
6 1	39	1 AVB alone	19	20	N.S
0 7	5	1 AVB + LBBB	4	1	—
0 7	4	1 AVB + RBBB	2	2	—
7 1	48	Total RBBB	26	22	N.S
5 3	40	RBBB alone	20	20	N.S
4 9	33	LBBB total	26	7	< 005
4 1	28	LBBB alone	22	6	< 005
1 9	13	Non specific IVCD	10	3	< 005
2 6	20	Q or QS in V_1	15	5	< 025
2 6	20	Q or QS in V_2	14	6	N.S
2 1	14	Q or QS in V_3	7	7	—
16 0	106	Non specific ST T changes	65	41	< 01
4 5	30	Unequivocal infarct	14	16	N.S
5 0	34	Atrial fibrillation	27	7	< 005
10 6	71	> 6 APS/min	39	22	N.S
11 0	74	> 6 VPS/min	41	32	N S

Electrocardiographic findings in 671 subjects age 70 or older are tabulated above and are grouped according to the presence or absence of clinical heart disease (CHD) The results of Chi square analyses when frequencies permitted are also given

†Abbreviations RAD = right axis deviation LAHB = left anterior hemiblock RBBB = right bundle branch block 1 AVB = first degree atrioventricular block LBBB = left bundle branch block IVCD = intraventricular conduction defect APS = atrial premature systole VPS = ventricular premature systole N S = not significant.

Unlike RBBB, LBBB showed a highly significant correlation with CHD (P < 005)

A Q or QS pattern in V_1 occurred in 20 cases Fifteen of these had CHD (P < 025) No age related distribution was noted

The ECG in 30 patients exhibited unequivocal evidence of myocardial infarction There was however, no relationship to CHD with an equal distribution of the abnormal ECG between the clinically normal and abnormal patients This discrepancy between unequivocal ECG evidence of myocardial infarction and clinically normal heart is in large measure due to the previously noted difficulty in obtaining reliable history in the aged

As far as arrhythmias were concerned only three types occurred in sufficient numbers to permit a statistical evaluation These include PVS in 11 per cent APS in 10 5 per cent and atrial fibrillation in 5 per cent Of these only atrial fibrillation correlated with CHD (P < 005) There was no correlation with any of the 16 drugs evaluated PVS were twice as common in males (P < 05) and also showed a tendency to increase in number with age (01 < P < 02) Other ECG findings too infrequent for significant analysis are included in Table IV

A frequency analysis of all variables was performed in subjects with normal ECG and CHD (147 subjects) and in patients with abnormal ECG and no CHD (124 subjects) attempting to discover if any distinguishing clinical characteristics existed in either group When patients with CHD were divided into groups with normal and abnormal ECG, congestive heart failure was found to occur with equal frequency in each (23

Table III Duration of P R interval and age*

Age (yr)	70 75	76-80	81 85	86 90	91 95	>95	P
Total	155	143	151	110	38	7	—
Mean P R	184	176	181	186	196	205	N S †
1 AVB (P – R ≥ 0 21 sec)	7	12	16	25	5	2	001

* P R intervals of 671 subjects are grouped above according to age Although no significant age related trends are apparent when mean P R intervals are compared, the incidence of first degree atrioventricular block (1 AVB) shows a highly significant increase with age

† N S = not significant

per cent) Thus in our population the presence of congestive heart failure appeared to have no significant correlation with the ECG Patients with CHD but normal ECG had a higher than expected incidence of irregular pulse on physical examination (P < 025) The arrhythmia because of its transient nature may not have been recorded in the ECG The presence of a systolic murmur was significantly more frequent in those with CHD and abnormal ECG (P < 001) When patients with normal ECG were separated according to presence or absence of CHD no significant trends in the ECG of either group were found

Discussion and review of the literature

In large measure the literature dealing with the geriatric ECG is derived from groups which are preselected. Some deal with patients without clinical heart disease[12-15] or on the other hand, include hospitalized or outpatient populations with a high incidence of heart disease[16,17]

The literature on the subject is conflicting For the most part these differences can be ascribed to (1) the lack of uniform criteria for defining the normal ECG and (2) inadequate sample size Pipberger and associates[18] have emphasized the importance of the latter by demonstrating that the correlation coefficient stabilizes only when the sample size is of sufficient magnitude Using the criterion of sample size alone only 4 previously reported studies may be considered to have adequate numbers[11,17,19,20]

In view of the large number of small series reported, an effort was made to combine these studies when possible in an attempt to determine the frequency of selected ECG abnormalities. These data are presented in Table V The size of the series ranged from 25 to 700 patients. Only reports dealing with patients 70

Table IV Electrocardiographic findings too infrequent for significance*

Electrocardiographic abnormalities	No.
Left ventricular hypertrophy	6
Left atrial predominance	5
Wolff Parkinson White syndrome	3
Sinus tachycardia	3
Paroxysmal atrial tachycardia	2
A V dissociation with interference	2
Sinus arrhythmia	2
Sinus bradycardia	2
Junctional rhythm	2
Atrial flutter	1
Multifocal atrial tachycardia	1
Mobitz I A V block	1
Complete heart block	1
Wandering atrial pacemaker	1
Right atrial predominance	1

* Samples not large enough for statistical analysis

years of age and older were included in this review The patients in the 19 series compared in Table V were not preselected for heart disease or electrocardiographic abnormalities Most were occupants of nursing homes or were noncardiacs attending outpatient clinics Several series however did consist of patients who were hospitalized for non cardiac reasons[14,16,17,21]

These findings are further compared with our own series and with those of Johnson and associates[22] and Manning[23] dealing with large numbers of young healthy males

A difference of 5 per cent between the combined series from the literature and our patients was assumed to be significant, and was found applicable to three variables, namely clinical evidence of heart disease abnormal ECG and specifically left axis deviation However this difference may be more apparent than real

Table V Frequencies of abnormal ECG, clinical heart disease and other ECG abnormalities obtained from the literature and compared to our present series and to normal young adult males

Entity	*Series reviewed (Age >70)*	*Total N*	*Frequency (%)*	*Present series (N = 671)*	*Frequency in normal young males*
CHD	12 13 15 16 17 21 37 38 66 71 72	1 801	1 055 (59%)	331 (49%)	–
Abnormal ECG	12 17 19 21 34 35 37 38 64 66 72	2 482	1 411 (52%)	306 (46%)	–
Atrial fibrillation	12 13 15 16 17 19 21 32 38 66 72	2 310	188 (8%)	34 (5%)	–
ALAD	12 13 15 16 32 38 72	1 190	611 (51%)	74 (11%)	0 10%[23]
RAD	12 13 15 16 32 38 72	1 190	14 (2%)	6 (1%)	–
1 AVB	13 15 17 31 32 34 35 37 66 72 73	3 145	292 (9%)	67 (10%)	0 52%[22]
RBBB	15 16 19 21 32 37 38 72 73	2 037	107 (5%)	54 (8%)	0 16%[22]
LBBB	15 16 19 21 32 37 38 72 73	2 037	55 (3%)	33 (5%)	0 02%[22]
APS	15 38 72	502	449 (10%)	71 (10%)	0 49%[22]
VPS	15 38 72	502	29 (6%)	74 (11%)	0 62%[22]
ST T changes	17 21 32 37 38	1 435	227 (16%)	128 (19%)	0 86%[22]

Abbreviations CHD = clinical heart disease ALAD = abnormal left axis deviation RAD = right axis deviation 1 AVB = first degree atrioventricular bundle block RBBB = right branch block LBBB = left bundle branch block APS = atrial premature systole VPS = ventricular premature systole

because of the difference in criteria from study to study

Clinical evidence of heart disease

Most large epidemiologic studies indicate the incidence of heart disease in the geriatric population ranges from 10 to 30 per cent and is two to three times as frequent as in groups under the age of 65[24,26] Our own experience suggests that 49 percent of the population studied had clinical evidence of heart disease This rather high incidence can probably be ascribed to both the difference in clinical criteria as well as a slight bias in favor of heart disease that is intrinsic to an institutionalized population It must be emphasized at this point that the history the most important part of the clinical evaluation is often unreliable in an elderly patient and represents a major problem in all clinical studies involving geriatric subjects This would explain the high incidence of unequivocal ECG evidence of myocardial infarction in clinically ' normal subjects

Abnormal electrocardiogram

Because of differing criteria from study to study the incidence of abnormal ECG s in the aged is also difficult to ascertain Of the 2 482 subjects selected from literature who were 70 years or older 52 per cent had an abnormal ECG (Table V) Further breakdown of this group will be described below

It has been pointed out that the type of heart disease found in the elderly is somewhat different from that predominating in middle age[27,28] Hardier individuals with more benign forms of heart disease tend to survive into old age Likewise, the clinical expression of heart disease is attenuated by the decreased physical demands made on the elderly One might expect then, that the age range of a sample population could affect the incidence of both CHD and ab

normal ECG However no significant differences were noted in any of the variables analyzed which could be attributed to the inclusion of the 65 to 70 year age group Too few geriatrics studies which included patients under 65 were available for analysis

Prognosis of abnormal ECG in the elderly

It would indeed be clinically useful if certain arrhythmias or patterns in the geriatric ECG could be positively or negatively correlated with the severity of heart disease and survival However examination of the literature reveals that no such correlations exist The prognosis of a specific ECG abnormality is essentially that of the underlying heart disease [29]

Unfortunately few longitudinal studies are available on geriatric populations In 1948 Fox[30] reported a 7 year follow up on 100 patients, one third of a group originally studied in 1939 All of the 100 subjects had normal tracings initially ST T wave changes were the most common abnormality that developed during the follow up and, in the majority of cases the development of an abnormal ECG was not associated with the development of CHD The mortality rate was slightly higher in the group that developed ECG abnormalities but cardiomegaly appeared to play a more important prognostic role in this group Rodstein Brown and Wolloch[31] studied 44 individuals with newly developed 1 AVB out of a group of 417 individuals Of these patients 34 had clinical diagnosis of coronary artery disease and 10 had evidence of digitalis intoxication The over all mortality rate was almost identical to that computed from actuarial tables even though one third of these patients had associated bundle branch block and 6 progressed to permanent second or third degree A V block

QRS voltage and axis changes

Several epidemiologic studies have shown that the R and S wave amplitudes decrease with age while the mean QRS vector rotates to the left in the frontal plane and posterior (or clockwise) in the horizontal plane [2,5,32,33] The T vector and spatial angle between T and QRS have been evaluated, but the relationship was inconsistent. It has also been demonstrated that other factors such as obesity produce effects that are similar to those of age [6] The less pronounced effect of age on voltage in females seems to become less apparent after the age of 40 [33] However, the bulk of the population from which the above findings were derived was less than 70 years of age

What information is available on the older age groups? Leftward shift of the frontal QRS axis and low voltage of R and S waves have been found to be quite common in geriatric populations [14,16,19,34,38] In 1953 Olbrich and Woodford Williams[39] reported a study which compared the effects of change in body position on the ECG both in young and aged subjects Elevating the thorax 45 degrees from the horizontal plane resulted in changes in R wave amplitude in all members of the elderly group but as many as 40 per cent of those younger than 30 showed no change at all Positional changes in P and T wave amplitudes were also quite exaggerated in the older group By altering position changes up to fivefold were obtained in R wave amplitudes recorded in V_5 and V_6 The appearance of Q waves and changes in the transitional zone were likewise more prominent in the elderly population with changes in body position The authors interpreted these findings as due to a greater freedom of motion of the heart within the thorax in the elderly patient Several mechanisms have been traditionally suggested as an explanation for this phenomenon (1) progressive development of kyphoscoliosis with increasing AP diameter (2) lowering of the diaphragms due to pulmonary emphysema (3) loss of the elasticity and increased resistivity of the tissues surrounding the heart and (4) elongation of the aorta

However abnormal left axis deviation (ALAD) defined as −30 degrees or beyond cannot be attributed solely to positional changes [40,41] Several autopsy studies have shown a strong correlation between anatomical changes and the presence of ALAD [42-44] On the other hand, epidemiologic surveys and some retrospective studies have failed to corroborate these findings [2,45,46] In an effort to reconcile these differences Ostrander[47] analyzed data from the Tecumseh study and found 248 subjects over age 20 with ALAD Of these 59 per cent had other associated ECG abnormalities suggestive of heart disease However in the 41 per cent with isolated ALAD followed for a period of four years no significant increases in heart disease morbidity mortality rate or risk factors were noted when compared

to the general population Michie[48] found no history of cardiac disease in 19 elderly men with isolated ALAD

However, there is some evidence to suggest that ALAD in the aged may be associated with heart disease Gorman and associates[49] determined the mean frontal plane QRS axis in 658 subjects between 60 and 94 years of age The group was divided evenly between the two sexes The incidence of ALAD increased with age only in the group that exhibited heart disease The frequency of other associated ECG findings was not reported, so that the frequency distribution of isolated ALAD in this particular study is not known Our data reveal an insignificant association of ALAD with clinical heart disease in the aged, but a significant increase in frequency with age

Left ventricular hypertrophy (LVH)

In the Framingham study, ECG evidence of LVH was more frequent in males and increased with age[50] That same study also revealed a strong relationship of LVH to hypertension and suggested that LVH is a poor prognostic sign even in the absence of clinical evidence of heart disease[51,52] Comparison of geriatric studies is again difficult due to differing criteria used for the diagnosis of LVH and clinical heart disease However, most of the studies reviewed show a positive correlation with heart disease Using the criteria of Romhilt and Estes[53] we diagnosed 6 cases in our own population all of which had CHD These criteria are conservative, resulting in 40 per cent false negatives but only in 3 per cent false positives In summary then the prevalence of ECG signs of LVH increases with age and is strongly correlated with heart disease

P R interval and first degree A V block

Some authors have noted a small but significant increase in the P R interval with age[4,54] but others have not[55-57] In their series of 67 375 young healthy pilots Johnson and associates[22] found a P R interval of > 20 sec in 5 per cent The frequency of first degree A V block (i e , P R > 22 sec) in the geriatric population is twice this figure (Table V) and our own experience is in close agreement

Life expectancy following the diagnosis of first degree A V block varies widely, depending on the underlying cause rather than on the presence of prolonged A V conduction[58] Only scant information on the epidemiology of first degree heart block is available in the aged. In one study no increase in mortality rate in 44 elderly subjects with 1° AVB was found.[31]

It would seem, then from the available data that although the frequency of abnormal P R prolongation is increased in the geriatric population its prognosis is dependent upon its etiology

Bundle branch block

The prognosis of bundle branch block (BBB) is dependent on its etiology[59] In a series of young healthy males, 02 per cent were found to have left bundle branch block (LBBB) and 16 per cent had right bundle branch block (RBBB)[22] Ninety three cases were found in the Framingham study[60] with approximately equal number of right and left BBB In that study individuals with either type of BBB had a higher mortality rate from cardiovascular disease Eighteen cases of RBBB and 18 of LBBB were reported from the Tecumseh study[61] Sixty seven per cent of the cases occurred in the 11 per cent of individuals past the age of 60 Twenty five cases had no clinical evidence of heart disease The prevalence of hypertension hypercholesterolemia hyperglycemia and obesity were high but not different among matched patients with normal ECG Edmands[62] reviewed 1,160 ECG s of subjects over 60 and found that 3 7 per cent had complete BBB Nineteen had LBBB and 38 had RBBB Cardiomegaly was associated with both types but was most frequent in those with LBBB No association with hypertension was found Uncomplicated RBBB was not associated with an increased incidence of heart disease However RBBB associated with ALAD did show a high degree of correlation with hypertension cardiomegaly, and congestive heart failure Review of the geriatric literature (Table V) reveals a combined BBB incidence of 8 per cent

In summary it appears that the incidence of both right and left BBB increases with age and they are most likely acquired defects There is an increased incidence of heart disease in patients with LBBB With respect to RBBB evidence suggests that when uncomplicated it is benign and only when it is associated with ALAD is it accompanied by an increased incidence of heart disease

Non specific ST T wave changes

Although non specific ST T wave changes can be due to a host of non cardiac causes there seems to be a significant association with heart disease Four hundred twenty two clinically normal males age 40 to 69 with minor ST T wave changes were subsequently found to have twice the incidence of coronary occlusion and total mortality rate than a matched control group[63] In the large series of young male pilots (Table V) ST T wave changes were evident in 0 86 per cent.[22] On the other hand an incidence of nearly 16 per cent was noted in 1 435 subjects over 70 from 5 comparable series in the literature[17,21 32 37 39]

This abnormality occurred in 19 per cent of our patients. A significant correlation of ST T wave changes with hypertension hyperglycemia and obesity has been found in men over 40 and with hyperglycemia in females over 40[32]

A review of the literature clearly indicates that the incidence of ST T wave changes is increased in subjects over 70 A consistent increase in the frequency through higher decades has not been found.[4 14,20 21,32,37,38 64] If non cardiac causes can be excluded the ST T segment changes in the resting ECG in the aged have the same prognostic implications as in the middle aged population

Myocardial infarction

Harris states that coronary thrombosis occurs in about 5 per cent of patients in geriatric wards[65] Examination of published data supports this estimate[15 34 37 64 66]

There is no data to suggest an age dependent relationship after the seventh decade Furthermore our population with ECG evidence of unequivocal infarction demonstrated no relationship to CHD (Table II) The large population of asymptomatic myocardial infarctions in our group may be related to the frequently unreliable history or less frequently to atypical presenting symptoms. A report of 387 cases of acute myocardial infarction in geriatric patients past 65 revealed that only 19 per cent presented with a classical onset.[67] Most of the symptoms were secondary to impaired myocardial function resulting in either exacerbation of preexisting conjestive heart failure or the development of symptoms of low cardiac output.

Atrial fibrillation

This arrhythmia occurred in 8 per cent of 2 310 patients reported in the literature and in 5 per cent of our group A higher frequency has been reported in hospitalized geriatric patients[68] Although it is universally considered an abnormal electrocardiographic finding the prognosis varies widely depending upon the specific etiology[69] Atrial fibrillation is more common in the geriatric population but no definite age related trend has been noted in patients over 70 Therefore when it appears de novo in elderly patients the differential diagnosis is essentially the same as in a younger individual with the following exceptions (1) a rheumatic etiology is less likely, and (2) it may often be the only evidence of apathetic hyperthyroidism a condition more frequently found in the aged.

Premature systoles

Premature systoles are among the most frequent rhythm disturbances encountered. Again as in the case in many other electrocardiographic findings, the prognosis is dependent upon the presence and the nature of underlying heart disease[0] Table V illustrates the marked increase in ventricular and atrial arrhythmias found in our population compared to the series of Johnson and associates[22] The frequency of about 10 per cent of both atrial and ventricular prematures found in our study is similar to that reported in the geriatric literature Since the incidence of heart disease increases with age one might assume that benign premature beats occur less frequently in the geriatric population The information presently available in the literature is inconclusive Fox and associates[34] found an increased incidence of hypertension and other ECG abnormalities associated with the presence of premature systoles. However this relationship was not borne out in a subsequent study[35] In their review of 322 aged Puerto Ricans Suarez and Suarez[38] found an increased number of atrial premature systoles in a group of patients suspected of having heart disease as compared with a group of healthy age matched controls Our study revealed no significant correlation of premature systoles and CHD (Table II) To date there are insufficient data to permit a clear definition of the clinical prognostic significance of premature systoles in the elderly patient.

Other ECG abnormalities

ECG abnormalities other than those already described occurred too infrequently in the geriatric population to permit a statistical correlation with heart disease or age Table IV lists *all of the electrocardiographic findings* including arrhythmias, found in our study but too few to subject to statistical analysis Gelfand[11] reported 20 cases of cardiac arrhythmias in geriatric patients and suggested that they must be an early manifestation of heart failure Two thirds of these patients had atrial fibrillation Taran and Szilagyi[20] found an increase in the frequency of total atrial arrhythmias from the seventh to the tenth decade

The low frequency of disturbances such as Mobitz type II A V block complete heart block, and multi focal atrial tachycardia in the geriatric population may seem surprising, but the serious prognosis of these arrhythmias is probably the reason for their rarity

Summary and conclusions

The literature concerning the geriatric ECG has been reviewed and some additional data presented The incidence of abnormal ECG increases with age as does the incidence of clinical heart disease (CHD) The manifestations of heart disease found in the elderly appear less severe when compared to that found in middle *age This is probably due to (1) the decreased* physical demands and (2) natural selection those with less severe forms of heart disease surviving to old age

In general the sex differences in the ECG abnormalities present in younger age groups are absent in the elderly Conclusive evidence as to the clinical *significance of isolated ALAD is as* yet lacking There is a tendency toward leftward axis shift and clockwise rotation ECG abnormalities that are found with increased frequency in the aged are 1°AVB ALAD LVH BBB ST T wave changes atrial fibrillation and premature systoles However, with the exception of LVH and possibly *ALAD the prognosis of each of* these conditions is that of the underlying disease

Our own data supports results of previous studies Of the 16 drugs examined only digitalis showed a statistically significant association with ECG abnormalities We found a highly significant association between *CHD and LBBB*, non specific IVCD, and atrial fibrillation LAH, Q or QS pattern in V_1, and non specific ST T wave changes also showed a significant association with CHD but to a lesser degree In our population, congestive heart failure was not necessarily associated with an abnormal ECG The presence of a systolic murmur increased the *likelihood that the patient would have both* CHD and an abnormal ECG Subjects with CHD but normal ECG s had a higher than expected incidence of irregular pulse at the time of physical examination indicating that paroxysmal arrhythmias may have been missed on the routine ECG

Both our data and that reviewed *from the literature* indicate that no modification of ECG *criteria is warranted for the aged* Indeed the close parallel between the incidence of abnormal ECG and CHD with age found in our study (Fig 2) suggests that the ECG may be a highly reliable indicator of heart disease even in the ninth and tenth decades when the validity of other parameters such as the history is often diminished However the *prognosis is that of* the underlying etiology rather than of the ECG abnormality per se

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Calcification of prosthetic valve anuli
A late complication of cardiac valve replacement

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The known late complications of cardiac valve replacement include thrombosis infection peribasilar valvar leaks endocardial fibrosis embolism and degeneration of materials of the prostheses [1] Another late complication previously undescribed is calcification at the sites of attachment of prostheses This report describes this complication in eight necropsy patients

Patients and results

Cardiac findings were reviewed in 96 necropsy patients who died more than 2 months after replacement of one or more cardiac valves with rigid framed prostheses (usually Starr Edwards prostheses) Seventy two patients with calcific deposits in the excised valves were eliminated 66 of them had had stenotic valves and six had had purely incompetent valves The remaining 24 patients, all of whom had had purely incompetent non calcified valves (aortic in 13 mitral in 13) form the basis of this report Isolated mitral replacement had been performed in 11 isolated aortic in 11 and both mitral and aortic in two The prosthetic implantation periods in the 24 patients ranged from 3 to 116 months (average 32) (Table I) Of the 13 patients with aortic prostheses two had calcific deposits at the sites of attachment of the prostheses their valve implantation periods were 12 and 70 months respectively Of the 13 patients with mitral prostheses seven had anular calcific deposits and the implantation periods in six were 70 months or longer the implantation periods in the six patients without calcific deposits ranged from 3 to 12 months (average seven months) The average ages of the seven patients with (48 years) were similar to those of the six patients without (47 years) prosthetic anular calcium

The extent of prosthetic anular calcific deposits graded 1 to 4 (Fig 1) varied in the eight patients, but in all the deposits were located on and between sutures The sutures utilized in all patients were fabricated of braided Dacron covered with a film of Teflon The

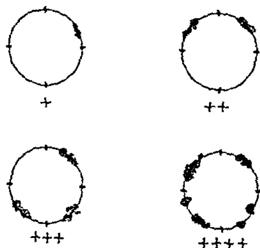


Fig 1 Extent of calcific deposits at site of attachment of prosthetic valve Scale of grading extent of periprosthetic anular calcium With 1 calcium is located in only 1 quadrant with 4 in all 4 quadrants

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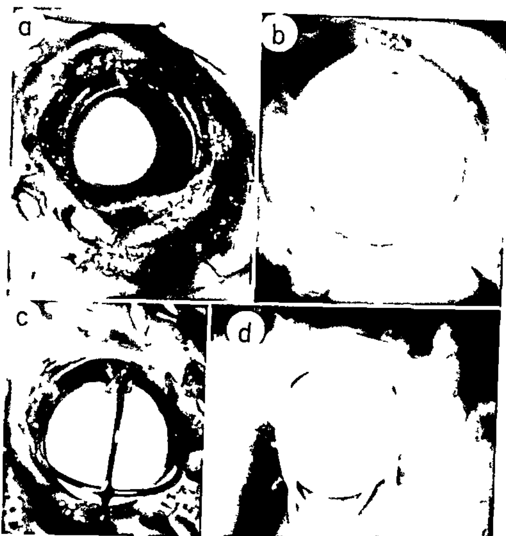


Fig 2 a through d Calcification of the Starr Edwards prosthetic mitral anulus in a 49 year old woman (A70 123) who underwent replacement 6½ years earlier The prosthesis viewed from left atrium (a) and (b) and from left ventricle (c) and (d) The radiographs show calcific deposits not visible grossly in the mitral anulus The calcific deposits are located primarily in and around sutures

deposits in several patients are illustrated in Figs 2 to 5

Comments

Calcification of prosthetic anuli is a late complication of cardiac valve replacement Of 26 previously non calcified purely incompetent valves excised 3 to 116 months (average 76) earlier calcific deposits developed around prosthetic anuli in nine Of the seven valves (one aortic six mitrals) in place for six years or more all had prosthetic anular calcific deposits Of the 13 patients with prosthetic mitral valves only one of seven with implantation periods of less than 70 months contained anular calcium but all six patients with implantation periods of more than 70 months contained anular calcium Of the 13 patients who had undergone aortic valve replacement only one had been in place for as long as 70 months and it contained prosthetic anular calcium Of the 12 patients with prosthetic aortic valves in place for less than 70 months one had anular calcific deposits

Calcification of the mitral anulus is frequently seen in elderly persons commonly in association with calcification of aortic valve cusps and coronary arteries and it is believed to be a consequence of the wear and tear of aging [2] Calcification in the mitral anular area may be accelerated however by conditions which elevate left ventricular pressure (systemic hypertension left ventricular outflow obstruction) [3,4] presumably because they increase wear and tear on the mitral valve Similarly constant to and fro motion of rigid framed prostheses may increase wear at the sites of attachment and accelerate the appearance of dystrophic calcification

Because its amount increases with time calcific deposits in prosthetic rings probably will

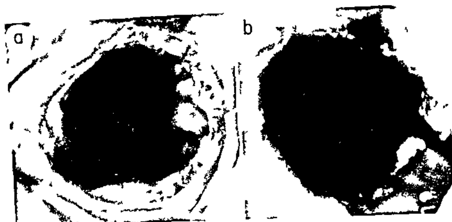


Fig 3 a and b Calcification of mitral anulus in a 49 year-old woman (A72 107) who died suddenly nine years after mitral valve replacement with a Starr Edwards prosthesis At necropsy the prosthesis showed no sign of dysfunction Shown is the mitral anulus (a) viewed from left atrium after the prosthesis was removed, and a roentgenogram (b) showing calcific deposits

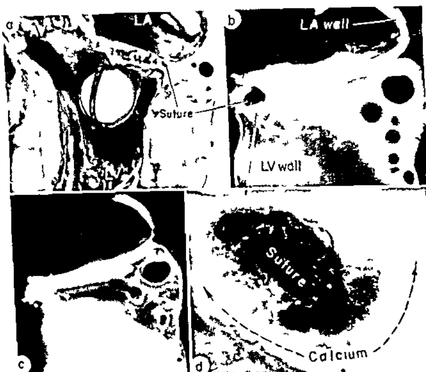


Fig 4 a through d Calcification of mitral anulus in a 45 year-old woman (A72 44) who died nine years after mitral valve replacement. Shown (a) is the left atrium (*LA*) left ventricle (*LV*) and the mitral prostheses Calcific deposits in the prosthetic anuli are seen on the radiograph (b) The prosthesis is held in place by sutures (c) and not by ingrown tissue Closer view of the suture (d) shows its encasement in a ring of calcium

become more common In none of our patients was prosthetic anular calcium visible by roentgenography during life but in none was the implantation period longer than 10 years. Possibly with longer periods the deposits might reach a degree visible by radiograph during life Calcific deposits in anuli might cause suture rupture and peribasilar leaks Ring calcification may be a hazard to reoperation to replace faulty prostheses

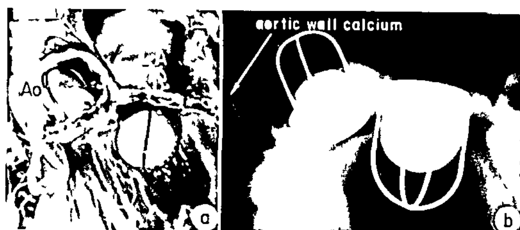


Fig 5 a and b Calcification of mitral and aortic prosthetic anuli in a 63 year old man (A72 30) who had undergone double valve replacements with Starr Edwards prostheses (size 4M and 11A) 70 months earlier A transverse section through the left heart shows left atrium (*LA*) left ventricle (*LV*) and aorta (*Ao*) A small peribasilar left ventricular-left atrial communication was present around the prosthetic mitral ring involving less than 10 per cent of the circumference of the mitral anulus Roentgenogram (b) demonstrates calcific deposits both in aortic and mitral prosthetic rings and in the aortotomy site The other patient with double valve replacement had calcific deposits in the mitral but not in the aortic prosthetic anulus

Table I Occurrence of prosthetic ring calcification in patients dying late after replacement of non calcified purely incompetent valves with rigid framed prostheses

Mitral					*Aortic*				
Patient	*Age (yr)*	*Sex*	*Prosthetic implantation period (mos)*	*Calcium prosthetic anulus (0-4+)*	*Patient*	*Age (yr)*	*Sex*	*Prosthetic implantation period (mos)*	*Calcium prosthetic anulus (0 4+)*
A69 62	65	M	3	0	A63 170	26	M	3	0
A69 292	44	F	4	0	A71 78	51	M	5	0
A71 32	55	M	7	0	A67 197	52	M	8	0
A68 197	52	M	8	0	A68 89	33	M	8	0
A67 119	49	F	9	0	A70 226	49	M	11	0
A66 54	15	F	12	0	A71 197	29	M	12	++
A67 118	47	M	44	++	A66 6	27	M	13	0
A72 30	63	M	70	+++	A67 7	53	M	14	0
A70 123	49	F	79	+++	A67 107	50	M	30	0
A70 10	57	F	80	++	A71 138	30	M	35	0
A72 107	49	F	105	++++	A67 118	47	M	44	0
A72 44	45	F	111	++++	A72 36	62	M	52	0
A72 88	29	F	116	+++	A72 30*	63	M	70	+++

*Aortic and mitral valves replaced

Summary

A previously undescribed late complication of cardiac valve replacement is calcification at the site of attachment of prostheses Of 24 patients in whom purely incompetent non calcified mitral or aortic valves were replaced with rigid framed prostheses 3 to 116 months earlier nine (seven mitral two aortic) of 26 valves had prosthetic anular calcific deposits Of the eight prostheses in place for 70 months or longer all contained anular calcific deposits only one of the 18 valves in place for less than 70 months had periprosthetic calcific deposits The extent of prosthetic calcium also increased with time The mechanism of formation of prosthetic anular calcium is uncertain but accelerated wear of

the tissues beneath the prostheses due to the constant to and fro motion of the rigid frames may be a factor Possible complications of prosthetic anular calcific deposits include suture rupture peribasilar leak and increased hazard to reoperation

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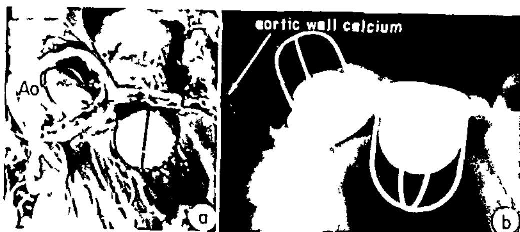


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A68 197	52	M	8	0	A68 89	33	M	8	0
A67 119	49	F	9	0	A70 226	49	M	11	0
A66 54	16	F	12	0	A71 197	29	M	12	++
A67 118*	47	M	44	++	A66 6	27	M	13	0
A72 30	63	M	70	+++	A67 7	53	M	14	0
A70 123	49	F	79	+++	A67 107	50	M	30	0
A70 10	57	F	80	++	A71 138	30	M	35	0
A72 107	49	F	105	++++	A67 118	47	M	44	0
A72 44	45	F	111	++++	A72 36	62	M	52	0
A72 88	29	F	116	+++	A72 30	63	M	70	+++

Aortic and mitral valves replaced

Summary

A previously undescribed late complication of cardiac valve replacement is calcification at the site of attachment of prostheses Of 24 patients in whom purely incompetent non calcified mitral or aortic valves were replaced with rigid framed prostheses 3 to 116 months earlier nine (seven mitral two aortic) of 26 valves had prosthetic anular calcific deposits Of the eight prostheses in place for 70 months or longer all contained anular calcific deposits only one of the 18 valves in place for less than 70 months had periprosthetic calcific deposits The extent of prosthetic calcium also increased with time The mechanism of formation of prosthetic anular calcium is uncertain but accelerated wear of

hypotensive anesthesia techniques Further permanent myocardial damage is rare following interruption of coronary blood flow for many minutes during cardiac surgery

Failure to pinpoint predictors of myocardial infarction indicates multiple or unknown factors at play This point of view is bolstered by a similar inability to indict any particular anesthetic or anesthetic technique as a primary cause of myocardial infarction Infarcts occur during or following general, regional or local anesthesia often in spite of apparently flawless technique Still as for many years the best advice is to avoid hypoxia and unstable blood pressure during and after anesthesia and surgery The immediate postoperative period has usually received scant consideration but it is now acknowledged that patients may be hypoxic as late as the third postoperative day following major surgery and fluid and electrolyte imbalance may persist for a similar or even longer period.

Various anesthetic techniques which minimize the chances of intra or postoperative hypoxia or cardiovascular instability are available Premedication should be individualized and adequate to insure tranquility but not so heavy as to depress respiration Moderate doses of a narcotic or barbiturate plus atropine or scopolamine usually suffice If a narcotic is to be a part of the anesthetic technique the first dose should be in the premedication since tachyphylaxis occurs to the hypotensive effect of the narcotics Likewise if a parasympatholytic drug is part of the premedication the incidence of arrhythmias following subsequent doses of atropine intravenously is greatly diminished. If the premedication is inadequate or regional or local anesthesia is to be used, the desired tranquility can be achieved in the operating suite by sequential doses of a narcotic intravenously before induction or nerve block

For operations on the extremities nerve block anesthesia is very satisfactory in the hands of an expert. The sciatic and other nerves can be blocked for operative procedures on the leg and brachial plexus block can be performed for procedures on the forearm or hand. Procedures in the neck such as thyroidectomy or carotid endarterectomy can be performed after cervical plexus block Spinal anesthesia is excellent for lower abdominal, perineal or lower limb procedures if care is taken to avoid hypotension Epidural anesthesia is often recommended because it takes effect more slowly than spinal block allowing more time to prevent or correct hypotension by infusion of Ringer s solution or judicious use of a vasopressor—preferably ephedrine Placement of a catheter permits continuous epidural anesthesia even into the postoperative period if this is desired for analgesia Block techniques permit adequate oxygenation avoid postoperative depression and in properly selected and prepared patients often provide the simplest and safest anesthesia

General anesthesia should include at least 50 per cent oxygen in the inspired gas mixture to provide a safety factor in case of airway obstruction or transient hypotension Cyclopropane and ethyl ether are excellent inhalation agents for poor risk patients but their use is often interdicted because of their flammability Halothane and enflurane are potent nonflammable inhalation agents and nitrous oxide has analgesic properties at 50 per cent concentration Any of these may be used as part of a balanced anesthesia technique Overdose of halothane and enflurane should be avoided since it is usually accompanied by hypotension

Thiopental has enjoyed wide use as a rapid, pleasant inducing agent which however may cause transient hypotension Another agent, ketamine is now available for this purpose with the advantage of not lowering blood pressure In fact it is contraindicated in hypertension because it may elevate blood pressure When used for induction only it is not hallucinogenic when the patient emerges from anesthesia following a procedure lasting 30 minutes or more It is possible to combine premedication an intravenous agent for induction and an inhalation agent for maintenance of light anesthesia with a curariform drug for muscle relaxation and achieve adequate oxygenation and a stable cardiovascular system throughout a long operative procedure on a poor risk patient. Reliance on an inhalation agent for maintenance insures minimal postoperative depression and over curarization can be avoided by monitoring degree of neuromyal block with a nerve stimulator The most widely used curariform drugs are succinylcholine by continous drip and d tubocurarine A new agent pancuronium is less apt to produce hypotension than d tubocurarine and, like the latter can be reversed by neostig

Anesthesia for the cardiac patient

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Myocardial infarction has long been a dreaded complication of anesthesia and surgery Many infarcts are silent or misdiagnosed so the actual incidence of this complication is difficult to estimate However two recent retrospective studies involving many thousands of patients indicate that the incidence of frank infarction postoperatively is about 0 1 to 0 2 per cent. Another recent prospective study on more limited numbers of patients suggests the same figure for incidence of patients with myocardial infarcts coming to operation and a postoperative infarction incidence of about 0 6 per cent About half of all infarcts—preoperative and postoperative—are undiagnosed Higher incidence rates have been reported but the figures are hard to compare because of the many factors involved such as age type of hospital diagnostic criteria pre existing disease etc The one point on which all agree is that the incidence of postoperative infarction is higher in patients with a previous infarction

Over all mortality rates of 20 to 83 per cent have been reported for patients who have incurred a postoperative infarction and when an infarct occurs in a patient with a previous infarction a mortality of 50 to 55 per cent may be expected It should come as no surprise that myocardial infarction after anesthesia and a major operation is more serious and deadly than myocardial infarction alone

Predictors for pinpointing the high risk patient would seem highly desirable A careful history and physical examination a preoperative ECG, and perhaps exercise tests for all surgical patients over 40 years of age would undoubtedly significantly reduce the number of undiagnosed old infarcts and other cardiac problems In patients with previous infarcts reinfarction is most likely when operation is performed less than three months later The reinfarction rate stabilizes at about 5 per cent after six months so elective surgery should be delayed beyond this time Of course many factors have been implicated in precipitating myocardial infarction during and after operation, especially a history of angina or hypertension the fact of being a male over 40 years of age and undergoing a thoracic or upper abdominal operation of longer duration than one hour The major pathophysiological factors involved are hypoxia hypotension or unstable blood pressure tachycardia hemorrhage or decreased cardiac output each obviously more significant against the high risk background. Certainly both anesthetist and surgeon will avoid these if possible in all patients and should proceed with extra caution when anesthetizing and operating on high risk patients

However, much of the above is based on clinical impression and statistical studies of varying reliability In a study of 225 patients with generalized vascular disease undergoing vascular surgery 3 myocardial infarcts occurred but no satisfactory predictors of myocardial stress were found Neither circulatory lability, degree and duration of hypotension during operation, duration of anesthesia and surgery, volume of blood replaced nor deviation from normal or preinduction blood pressure could be correlated with myocardial stress as assessed by ECG changes, blood enzyme and 5 isoenzyme values and clinical course Equally disturbing to the hypothesis that hypotension is a primary villain is the fact that the incidence of myocardial damage is not increased when systolic pressure is maintained at 60 mm Hg for many hours in

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Annotations

General anesthesia and myocardial infarction

Each year approximately 800 000 recognized myocardial infarctions (MI) occur in the United States[1] and the number of patients who have MI or coronary heart disease (CHD) and who require some form of surgery is increasing steadily as population increases These patients obviously present problems related to cardiac disease if they are subjected to the stress of general anesthesia and surgery

In spite of the incidence of MI and CHD among patients who require surgery there are few statistics relating to the incidence of primary or recurrent MIs after anesthesia and the existing data are based on a relatively small number of cases This study is an attempt to provide additional data by analyzing our own experience with such patients in a two year period

During the years 1967 and 1968 32 877 patients aged 30 years or more underwent some form of operation or diagnostic procedure in our institution Among these MI had occurred in 422 patients before operation, and reinfarction (indicated by clinical symptoms electrocardiogram enzyme studies, or postmortem examinations) occurred in 28 of them (6 6 per cent) during the first week of the postoperative period.

In addition, 43 patients with no previous history of MI had infarction after operation the incidence was 0 13 per cent of all the patients in this series having anesthesia. Among anesthetized patients, the incidence of previous MI was 1 28 per cent The incidence of previous MIs increased with age being highest at the eighth decade of life (2 79 per cent)

Of the 28 patients with reinfarction 15 died (54 per cent) In 12 of these patients (80 per cent) death occurred during the first 48 hours after MI which suggests that arrhythmias rather than a low cardiac output may be the primary cause of death. Since infarction occurred while the patients were in the hospital, it can be assumed that if all patients with coronary heart disease and previous MIs were monitored and arrhythmias were treated in the intensive care units soon after operation, the mortality rate would diminish.

Age of the patients duration of anesthesia and type of anesthetic agents used had no influence on the incidence of reinfarction

Among the 43 patients who had infarction after operation and who had no previous evidence of MI before operation, 16 had known CHD with angina In the other 27 patients there was no history of CHD but 6 were diabetic and 10 were being treated for hypertension. The mortality rate of these first infarctions was also high 29 (67 per cent) of them died, 20 (69 per cent) dying during the first 48 hours after infarction.

During and after an operation, MI may be precipitated by several factors such as tachycardia hypoxemia hypotension, hemorrhage and a decreased cardiac output.[2] These complications are more frequent after surgery of the great vessels, lungs, and upper abdomen. The incidence of infarction in patients having these operations was three times as great as in any other types of operations this indicates that it is especially important to maintain an optimal blood volume and blood pressure during and after operation in patients with previous CHD and MI

In 6 (21 per cent) of the 28 cases of reinfarction the reinfarction was silent it was discovered electrocardiographically after operation. Chest pain was absent or was obscured by narcotics and sedatives. Daily serial ECG tracings after operation and their comparison with base line ECGs taken before operation would improve the diagnosis of a silent MI occurring after operation

The shorter the interval between a previous MI and a major operation the greater the hazard of reinfarction would be[3] In our series 37 per cent of patients operated on within 3 months of myocardial infarction had postoperative reinfarctions The incidence decreased to 16 per cent in patients in whom the MI was 3 to 6 months old, and it stabilized at 5 per cent after 6 months These figures indicate that in a patient with a history of MI and who presents with a surgical disorder within 6 months of the infarction surgery should be considered only if the surgical emergency is life threatening

The relationship of MI to the day of its occurrence after operation varied but the incidence of MI was greatest on the third postoperative day After abdominal surgery arterial oxygen (O_2) tensions decrease for at least 3 days due to miliary atelectasis pulmonary shunting and possibly decreased cardiac output.[4] By increasing the inspired O_2 tension and by providing chest physiotherapy by coughing and by deep-breathing exercises, the incidence of atelectasis would be lessened, the myocardial O_2 supply would be kept adequate and possibly MI could be avoided in high risk patients Close observation and aggressive treatment after operation would make anesthesia and surgery relatively safer for such patients

Having studied our own data and those reported in the literature we believe that the risk to the patient who has had a myocardial infarction and who must have general anesthesia and surgery can be minimized by appropriate management Such patients should be transferred immediately after operation to an intensive care unit for continuous cardiac monitoring complete electrocardiograms daily for the first 3 days and administration of O_2 by mask, in addition to the routine care and aggressive therapy of dysrhythmia that are customary in such units

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mine if block persists following completion of the operative procedure

The use of morphine or other narcotic analgesics by the intravenous route for pain accompanying myocardial infarction is well accepted by cardiologists as a means of providing analgesia with minimal cardiovascular depression Anesthesia by the narcotic technique is an extension of narcotic analgesia which is widely used for poor risk patients The technique involves induction with sequential doses of a narcotic and 50 to 60 per cent nitrous oxide maintenance with nitrous oxide, a muscle relaxant, and sequential doses of narcotic as required Induction is relatively slow, hypotension is rare and respiratory depression caused by the narcotic is obviated by controlled ventilation At the end of operation residual narcotic depression can be reversed with the narcotic antagonist naloxone Morphine in doses of 1 to 2 mg per kilogram of body weight can be used if the patient is to have assisted ventilation overnight following operation Meperidine has a shorter duration of action and is so rapidly metabolized that some patients will not require reversal after 5 to 10 mg per kilogram of body weight used in 3 to 5 hour procedures Recently fentanyl a potent, rapid onset, ultrashort acting narcotic has become available an induction dose of 300 to 500 μg can be supplemented with 50 to 100 μg every 30 to 45 minutes. Thus the availability of narcotics with varying duration of action and a specific narcotic antagonist make the narcotic anesthetic technique extremely versatile and the pharmacological properties of the narcotics make them relatively safe in experienced hands.

In conclusion several regional and general anesthetic techniques are suitable for patients with a history of myocardial infarction who require an operation or special examination under anesthesia Elective procedures should be deferred for at least six months following an infarct and hypoxia and cardiovascular instability should be avoided during anesthesia and postoperatively Impeccable anesthetic and surgical technique close attention to fluid and electrolyte balance pre and postoperatively, and to oxygenation and ventilation postoperatively, are required to minimize the risk of myocardial infarction in high risk patients

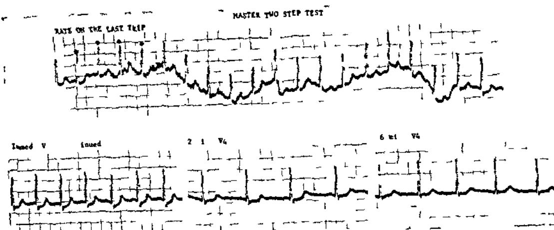


Fig 1 The illustration reveals the Master Two Step Test recorded on a patient (D B) a man aged 39 years with angina pectoris. The upper row shows the last trip being recorded in a V_4 lead. The heart rate is 150 beats per minute It gives the fastest rate attained in the two step test. The lower row shows the first immediate post exercise tracing in the same V_4 lead with a rate of 120 beats per minute Ordinarily this figure would be recorded as the fastest rate attained, whereas it is actually 150 beats per minute

The fastest rate attained in the Master Two-Step Test

Many investigators have expressed the opinion that the fastest heart rate attained in the Master Two Step Test is not high enough to demonstrate significant ischemic S T segment depression and therefore the heart has not been subjected to sufficient stress to study cardiac function We have papers in preparation to refute this theory

Meanwhile we would like to describe a method that can be utilized by the doctor with only an ordinary electrocardiograph machine (non monitored) to obtain the fastest *heart rate in the exercise (Fig 1) The rate is always fastest* during the last trip of the two step test. To record this rate the electrocardiograph machine should be flipped on just as the patient begins the last trip so that there is an immediate recording of the electrocardiogram This is essential because between the time the patient completes the test and lies down and is quickly readied for the immediate post exercise tracing 10 to 30 seconds may be lost during which time the highest rate as registered would have fallen 10 to 40 beats per minute Although this tracing will be unreadable from the point of view of the S T segment depressions the QRS will be delineated every time so that the correct rate can be measured

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Of viral nephritis

It is interesting that for many years the streptococcus *has* been considered to be almost the sole cause of acute glomerulonephritis This etiologic concept *has* prevailed despite the fact that most patients with the chronic forms of glomerulonephritis present no past history of acute glomerulonephritis or of a *streptococcus related* infection However one will not find things that are not sought. *Unless* the proper questions are asked, the proper answers will *not* be obtained. With these and other views in mind, we searched for a possible viral etiology of glomerulonephritis.

Mice and cynomolgus monkeys were infected with Coxsackie B_4 virus and acute and chronic glomerulonephritis were noted to develop (Fig 1)[1 2] *Histologic* and electron microscopic studies showed the renal lesions to have the same pathologic characteristics as lesions found in man suffering with acute and chronic glomerular lesions of

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Depression of cardiac output by sedation in congenital semilunar valve stenosis

Although physical examination and ancillary investigations are important in assessing the severity of congenital pulmonic and aortic stenosis decisions about surgical management often hinge on the hemodynamic findings at cardiac catheterization One of the most widely used premedication regimes has been a mixture of meperidine 25 mg per milliliter promethazine 6 25 mg per milliliter and chlorpromazine 6 25 mg per milliliter (MPC) given in a dose of 0 1 ml per kilogram of body weight to a maximum of 2 ml [1 3]

Having noticed depression of cardiac output below predicted values[4] in children with aortic and pulmonic valve stenosis studied after premedication with MPC we have recently utilized the neuroleptanalgesic agent Innovar (fentanyl and droperidol) for some studies.

As a preliminary gross assessment of these two regimes the deviation in cardiac output from predicted normal values was assessed in 86 children with aortic or pulmonic stenosis sedated with MPC and in 20 similar children sedated with fentanyl and droperidol

The normal values used were derived from studies in 38 normal children with no demonstrable cardiac disease or idiopathic dilatation of the pulmonary artery using either the Fick technique with measured oxygen consumption or dye dilution From these measurements regression equations based on age weight and height have been derived as previously described [4] The premedication regime for these normals was MPC

In 86 patients with aortic or pulmonic stenosis sedated with MPC cardiac output was depressed by a mean 16 7 per cent (standard error of mean 3 0 per cent) There was no difference in the depression of cardiac output between the 54 of these patients with pulmonic stenosis (mean 15 0 per cent S E M 3 9 per cent) and the 32 with aortic stenosis (mean 19 5 per cent S E M 4 5 per cent)

However in 20 similar patients sedated with fentanyl and droperidol the cardiac output was depressed by only 5 3 per cent (S E M 7 0 per cent)

The cardiovascular effects of meperidine are minimal in the supine position [5] Phenothiazines however produce peripheral vasodilation and act synergistically with narcotic analgesics to produce respiratory depression with secondary cardiovascular effects from hypoxia and hypercarbia [5] Goldberg and associates[6] found that in dogs MPC produced only a slight reduction in cardiac output but significant decrease in systemic and an increase in pulmonary vascular resistance Fentanyl and droperidol is thought not to produce significant hemodynamic changes [7] provided respiratory insufficiency is not produced [8]

These preliminary results serve to indicate once more that (1) ventricular pressures measured at rest with the cardiac output depressed by sedation are likely to be falsely low and the severity of the lesions underestimated (2) fentanyl and droperidol seems less depressant than MPC and if its sedative and analgesic effects are comparable (as they are in our experience) it should be used more often

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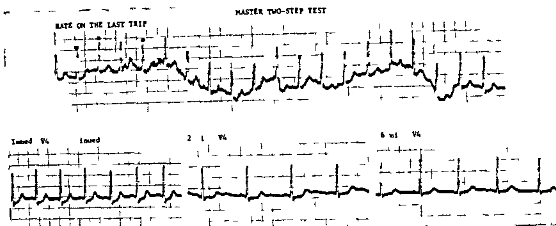


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Mice and cynomolgus monkeys were infected with Coxsackie B_4 virus and acute and chronic glomerulonephritis were noted to develop (Fig 1)[1,2] Histologic and electron microscopic studies showed the renal lesions to have the same pathologic characteristics as lesions found in man suffering with acute and chronic glomerular lesions of



Fig 1 Section of kidney from a young adult mouse 7 weeks after inoculation with Coxsackie B_4 virus The Bowman s capsule of the glomerulus at the left is thickened and there is hypercellularity of the glomerulus on the right of the illustration There is heavy aggregation of plasmal and lymphocytic cells in the renal interstices and destruction of tubules (Hematoxylin and eosin Original magnification ×200) (From Sun S C Burch G E Sohal R S and Chu, K C Coxsackie B_4 viral nephritis in mice and its autoimmune like phenomena Proc Soc Exp Biol Med. 126 882 1967 Reproduced with the permission of the publishers)

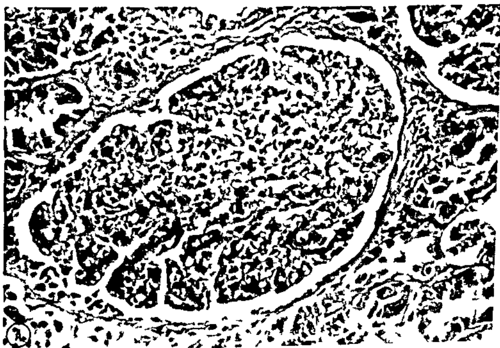


Fig 2 A and B Sections of kidney from a 75 year old woman with acute glomerulonephritis *A* Increased cellularity capsular thickening and leukocytic infiltration are evident (Hematoxylin and eosin Original magnification ×620) *B* There is indirect immunofluorescent staining with Coxsackie virus B_1 antiserum of cells (*arrows*) within the glomerulus (Original magnification ×780) (From Burch G E Chu K C Colcolough H L and Sohal R S Immunofluorescent localization of Coxsackie virus B antigen in the kidney observed at routine autopsy Am J Med 47 36 1969 Reproduced with the permission of the publishers)

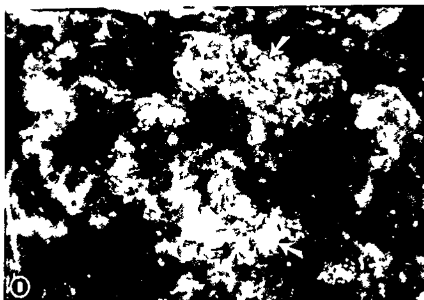


Fig 2B For legend see opposite page

glomerulonephritis. Sections of renal tissue of man gathered randomly at autopsy revealed immunofluorescent antibody staining for Coxsackie B antigen in the glomeruli (Fig 2) of kidneys displaying lesions of chronic glomerulonephritis[3] Thus these studies in experimental animals[1,2] and man[3,4] show that viruses will produce acute and chronic glomerulonephritis

Careful history taking reveals that many patients who have glomerulonephritis have had viral types of upper respiratory tract infections (U R I) The conditioning factors which determine whether or not a particular U R I will produce nephritis remain unknown. Important ones must exist To list some would have no more than conjectural significance Furthermore the relationship between viral and streptococcal infections in the production of renal diseases is also unknown This is due in large part to the lack of adequate viral diagnostic and service laboratory facilities in clinics and hospitals. Facilities for bacterial studies are available and are used rather extensively When streptococci are not found in throat cultures and ASO titers are not elevated in patients with U R I it is casually assumed that the streptococcus had been present previously or that the laboratory data are wrong This biased attitude is erroneous Viral and histologic and electron microscopic findings support the concept that nephrotropic viruses are responsible for glomerulonephritis

It is not surprising that viruses can produce renal disease when it is remembered that viremia is common and that the function of glomeruli is to filter out protein material including viral particles as glomerular filtrate is made With 20 per cent of the cardiac output flowing through the kidneys a concentration of viruses would be expected to develop in the glomeruli during a viral infection with viremia And if the conditioning factors are satisfactory glomerulonephritis would be expected to follow with all its manifestations and consequences Viruses are well known to grow readily on renal cell tissue culture media

The importance of such findings and concepts is self evident especially in view of the fact that viral vaccines could even be developed to prevent development of the viral nephritis Renal diseases of viral etiology need further investigation

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Letters to the Editor

Heparin and platelets

To the Editor

In the editorial entitled Heparin platelets and venous thrombosis (AM HEART J 85 435 1973) attention is focused on an important but complex subject The statement that heparin inhibits the platelet release reaction is not generally agreed upon In fact increasing evidence indicates that heparin itself has release promoting properties[1,2] and may enhance platelet aggregation induced by other agents[2-4] This effect of heparin may also be involved in the increased platelet adhesiveness and platelet fall observed during extracorporeal circulation[4] The inhibitory effect of heparin on platelet release observed in heparinized platelet rich plasma[2,3,5] is most likely secondary to previous heparin induced release[2,3]

The release promoting properties of heparin contrast the potent and specific inhibition exerted by small amounts of heparin together with antithrombin III on thrombin induced platelet aggregation[6] Whether the most important effect of heparin antithrombin III is the antithrombin or the anti factor Xa activity probably is still a matter of speculation As recently pointed out by Marciniak[7] the importance of antithrombin III as anti factor Xa may have been over emphasized The multifaceted effect of heparin on platelets is in accordance with the observed effect of heparin in clinical situations where thrombin generation is involved[8] and the failure of heparin to correct pathological conditions with primary platelet involvement[8] Some reports indicate that occasionally heparin may even enhance a thrombotic process[9-11]

The complex effect of heparin obviously needs further research to clarify the effect of this agent in different experimental and clinical situations

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Reply

To the Editor

Dr Eika suggests that heparin may not inhibit the release reaction He is writing in July 1973 and had access to the most recent reports including his own very relevant work[1] and that of Dr Zucker[2] and I think he now presents a fairer appraisal of the situation than I did in my review written in the summer of 1972 It is however of interest that Swank[3] in his special experimental conditions also found some evidence of inhibition of platelet function by heparin

One of the major problems in studying the effect of heparin on blood is to know with what kind of blood it should be compared Of course native blood is ideal but this is not often possible Anticoagulation by citrate removes most of the free calcium ions and so inhibits to a considerable extent many of the adhesive properties of platelets Thus platelets in heparin will often appear more reactive than platelets in citrate A further problem is the development of a refractory state when platelets stimulated for example by ADP first become more reactive and subsequently less reactive than they were before adding the ADP Thus, if in a given experiment a lesser reaction is obtained with heparin it could always be explained by the development of a refractory state due to previous stimulation

I agree with Dr Eika that the complex effect of heparin obviously needs further research If tiny doses of heparin (5000 U b d) can be shown to inhibit clinical as well as isotopically detectable thrombosis then heparin clearly will have a most important lesson still to teach us about thrombosis Indeed it would be surprising if such a highly charged molecule did not have many effects and I agree it may well not act only as an anti factor Xa

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American Heart Journal

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Editorial

Some cardiovascular effects of cannabis

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It has been estimated that some 250 000 000 people throughout the world at the present time have had experience of marijuana smoking Yet despite this widespread use the many published observations on its effects consist mainly of descriptions of subjective phenomena and most of these have been made in psychiatric or social contexts The available laboratory studies—whether in animals or man—are in the main related to some special interest of the investigator concerned

Probably because it lacks any apparent therapeutic application no serious attempt has been made by the pharmaceutical industry or by the responsible scientific community to study systematically the effects of marijuana smoking on body systems nor has it been submitted to the routine battery of tests imposed on any chemical compound before it becomes generally available However notwithstanding its legal status and irrelevantly of any opinion we may hold concerning its present social use an attempt must be made to study and evaluate cannabis in a manner similar to that carried out on any other drug which is readily available and widely used.

These comments are prompted by an incident that took place while I was in India in 1966 and by the interest which I have taken in the subject since then During this Indian visit at the local university hospital I was shown a young man in a coma I could find no obvious cause for this condition He was warm although his rectal temperature was low (35 5° C) His pulse was 100 per minute and full and regular My Indian colleagues told me that he was suffering from an overdose of cannabis and that they saw a few similar cases every year If patients were admitted in the very early stage of intoxication cardiac arrhythmias were often recorded including various degrees of A V block later tachycardia supervened. Spontaneous recovery in 24 to 48 hours with no specific treatment was the rule and no late ill effects had been reported

To my surprise a thorough search of the literature made on my return home revealed few reports of quantitated cardiovascular or other physiologic responses to marijuana smoking By chance the opportunity arose to investigate some cardiovascular effects while on a further visit to the Middle East last year

Studies were conducted on volunteers aged between 30 and 40 years who had no previous experience of cannabis We found that in all our subjects there was a marked increase in limb blood flow more pronounced in the muscle beds than in those of the skin[1] This increase in peripheral flow was not accompanied by a fall in arterial blood pressure suggesting circulatory adjustments including alterations in blood flow in other vascular beds and the low rectal tem

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Rec v d for p blic t on Nov 16 1972.

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Heparin and platelets

To the Editor

In the editorial entitled Heparin, platelets and venous thrombosis (AM HEART J 85 435 1973) attention is focused on an important but complex subject The statement that heparin inhibits the platelet release reaction is not generally agreed upon In fact increasing evidence indicates that heparin itself has release promoting properties[1,2] and may enhance platelet aggregation induced by other agents[2-4] This effect of heparin may also be involved in the increased platelet adhesiveness and platelet fall observed during extracorporeal circulation[4] The inhibitory effect of heparin on platelet release observed in heparinized platelet rich plasma[2,3,5] is most likely secondary to previous heparin induced release[2,3]

The release promoting properties of heparin contrast the potent and specific inhibition exerted by small amounts of heparin together with antithrombin III on thrombin induced platelet aggregation[6] Whether the most important effect of heparin antithrombin III is the antithrombin or the anti factor X[a] activity probably is still a matter of speculation As recently pointed out by Marciniak[7] the importance of antithrombin III as anti factor X[a] may have been over emphasized The multifaceted effect of heparin on platelets is in accordance with the observed effect of heparin in clinical situations where thrombin generation is involved[8] and the failure of heparin to correct pathological conditions with primary platelet involvement[8] Some reports indicate that occasionally heparin may even enhance a thrombotic process[9-11]

The complex effect of heparin obviously needs further research to clarify the effect of this agent in different experimental and clinical situations

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Reply

To the Editor

Dr Eika suggests that heparin may not inhibit the release reaction He is writing in July 1973 and had access to the most recent reports including his own very relevant work[1] and that of Dr Zucker[2] and I think he now presents a fairer appraisal of the situation than I did in my review written in the summer of 1972 It is however of interest that Swank,[3] in his special experimental conditions also found some evidence of inhibition of platelet function by heparin

One of the major problems in studying the effect of heparin on blood is to know with what kind of blood it should be compared Of course native blood is ideal but this is not often possible Anticoagulation by citrate removes most of the free calcium ions and so inhibits to a considerable extent many of the adhesive properties of platelets Thus platelets in heparin will often appear more reactive than platelets in citrate A further problem is the development of a refractory state when platelets stimulated for example by ADP first become more reactive and subsequently less reactive than they were before adding the ADP Thus if in a given experiment a lesser reaction is obtained with heparin it could always be "explained" by the development of a refractory state due to previous stimulation

I agree with Dr Eika that the complex effect of heparin obviously needs further research If tiny doses of heparin (5000 U b d) can be shown to inhibit clinical as well as isotopically detectable thrombosis then heparin clearly will have a most important lesson still to teach us about thrombosis Indeed it would be surprising if such a highly charged molecule did not have many effects and I agree it may well not act only as an anti factor X[a]

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for about 60 minutes While smoking and for about 30 minutes thereafter some increase in width and diminution in amplitude of the P wave in Lead II was observed, and in Lead III the T wave was inverted. The tremor could be the result of cannabis effect on muscle repolariza tion with a consequent change in impulse travel from atria to ventricles evidenced by the change in P and T waves All these findings could be the result of alterations in blood flow through the myocardium

The direct cardiac effect of THC was studied in the guinea pig heart lung preparation left in situ but isolated from all endogenous in fluences—hormonal nervous etc The following parameters were measured cardiac output rate and ECG With doses similar to those ad ministered to the intact animal there was no change in cardiac function The dose was then progressively increased to fourfold and then to tenfold, still with no change Only when the dose was increased to fiftyfold did major changes of progressive cardiac insufficiency with bradycar dia begin to appear and these effects worsened as the dose was further stepped up

In the intact animal under similar conditions within 2 to 4 seconds of the massive intravenous dose there was a sharp decrease in ECG voltage and a fall in sinus rate of about 25 per cent This progressed in most instances to a 2 1 atrio ventricular block and within 2 to 4 minutes of the injection ventricular tachycardia super vened Intermittent sinus rhythm returned gradually and by around 6 minutes there was complete recovery of sinus rhythm and a return towards normal in the ECG voltage The animals were allowed to recover and none of them showed any apparent ill effects This seems to suggest that whatever the nature of the toxic effect on the myocardium is it is effectively and rapidly dealt with by general metabolism in the intact animal

All these responses were still evoked after a premedication dose of atropine but did not occur in subjects given a course of propranolol—a beta adrenergic blocker The tachycardia pro duced by both atropine and epinephrine was po tentiated by marijuana

Extensive blood profiles and comprehensive urinalyses before and after marijuana smoking in our volunteers were also established The only changes we recorded were some fall in plasma growth hormone levels and an increase in the thiamine pyrophosphate effect immediately after smoking both returned to control levels within a couple of hours Evidence of stimulation of epinephrine production by marijuana was not elicted levels of blood glucose lactate pyruvate and fatty acid fractions were unchanged by smoking Although the usual diuresis after can nabis smoking pertained urinary constituents as measured in mEq per hour were unchanged, except for a slight increase in sodium and chloride excretion

There is no doubt that in the near future there will be changes in the legal status of pot, and some relaxation in the penalties for its posses sion and use The subject has been engaging government appointed committees on both sides of the Atlantic for some time recently and the World Health Organization and the National Institutes of Health have put out at different times recommendations stressing the need for a thorough investigation of *Cannabis sativa.*

A considerable volume of research is presently going on into the subject most of it supported by public money While all information is of value in adding to our knowledge a proper investiga tion of marijuana is not a research project in the classical sense disseminated among various laboratories according to the principal interest of their directors What we need to know should be found out by submitting marijuana to the kind of testing protocol pharmaceutical houses have to put all drugs through before they can submit a dossier to the F D A or to the British Medicines Commission for permission to market Such a project should be delegated to a laborato ry where drug testing of an industrial nature is routinely done Everything else is a luxury which we cannot afford in the present state of our knowledge From such a technical investiga tion into *Cannabis sativa* we would have a full spectrum of the physiologic and biochemical effects of the compound, and in addition infor mation on its possible therapeutic effects Of the latter its antihistaminic and diuretic actions seem worthy of further study It is incredible but true that some systematic pharmacological in vestigations were carried out by Hardman and colleagues[4] under contract with the Army Chemical Center as far back as the late 1950 s and that the results of their studies were classified as security information with permis

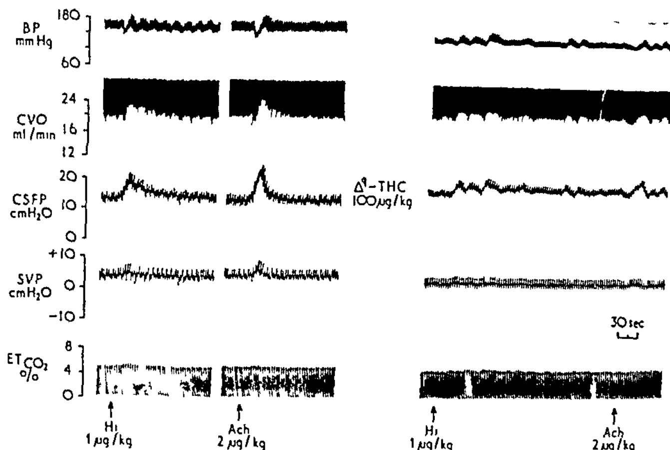


Fig 1 Simultaneous recording of histamine and acetylcholine response before and after administration of THC *BP* = blood pressure in femoral artery *CVO* = cerebral venous outflow as measured from the confluence of sinuses *CSFP* = cerebrospinal fluid pressure measured in the cisterna magna *SVP* = systemic venous pressure $ETco_2$ = end tidal concentration of CO_2

perature reading mentioned earlier lends support to this conjecture The tachycardia invariably present after marijuana smoking is itself another evidence of adjustment And this is further supported by our finding that cannabis has no direct effect on the myocardium [2]

An intravenous dose of the main active constituent of *Cannabis sativa* delta 9 tetrahydrocannabinol (hereafter abbreviated as THC) of the order of 100 μg per kilogram of body weight increased the pressure of the cerebrospinal fluid, but variations in the cerebral blood flow as measured directly from the confluence of sinuses by the venous outflow technique, were small and inconsistent [3] Changes in this outflow can be considered indicative of changes in intracranial blood flow and in the main reflect the behavior of the resistance vessels while changes in cerebrospinal fluid pressure essentially reflect the behavior of the capacitance vessels

During our studies on the volunteers, two of them who had colds at the time reported decrease in coryza and nasal decongestion after smoking marijuana To investigate the validity of this being a possible antihistamine type response animals in which histamine and acetylcholine had evoked a fall in arterial blood pressure with a subsequent compensatory rise were then given intravenous THC, and administration of the same dose of histamine and acetylcholine as before was repeated This time there was no fall in blood pressure after histamine and only a slight reduction after acetylcholine Venous pressure was also increased by injection of histamine and acetylcholine in the control period, but was unchanged when these agents were administered after the injection of THC A similar trend was observed in respect of cerebrospinal fluid pressure and central venous outflow, the rise induced by histamine being virtually abolished after the TCH, and that to acetylcholine reduced (Fig 1)

ECG tracings were done on our volunteers before and after marijuana smoking [1] The tachycardia induced by cannabis was sinus in origin During smoking a tremor appeared on the tracing in a number of subjects and persisted

Hemodynamic response to supine exercise in patients with chest pain and normal coronary arteriograms

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A vast majority of patients with chest pain suspected to be secondary to coronary artery disease (CAD) display significant obstructive disease of the coronary arteries on angiography Yet a sizable number of subjects with chest pain are found to have entirely normal coronary arteriograms A careful medical evaluation prior to cardiac catheterization usually identifies those subjects with definite cervical radiculitis costochondritis pericarditis or gastrointestinal problems as the cause of chest pain Cardiac catheterization has demonstrated that some of the remaining patients have abnormal resting intracardiac pressures and/or an abnormal left ventriculogram and they are classified as having primary myocardial disease However a group remains that does not display left ventricular abnormalities at rest and is usually said to be normal The chest pain is described as functional or musculoskeletal in origin With the intent to determine whether these patients with chest pain of uncertain etiology exhibit entirely normal cardiac function we have studied their response to supine exercise at the time of cardiac catheterization

Materials and methods

Patients During 1971 234 patients were studied in our laboratory for various cardiovascular abnormalities After excluding subjects with (1) prior myocardial infarction documented by definite electrocardiographic abnormalities and/or serum enzyme changes (2) valvular heart disease (3) congenital heart disease and (4) obvious cardiomyopathy as shown by clinical and hemodynamic studies there remained a group of 58 patients whose chief symptom was chest pain suspected to be secondary to CAD Within this group of 58 patients 32 patients revealed 50 per cent or greater narrowing in one or more coronary arteries 9 were classified as having cardiomyopathy on the basis of abnormal resting intracardiac pressures and/or abnormal left ventricular contraction on angiography and 8 patients were found to be entirely normal The remaining 9 patients who displayed an abnormal hemodynamic response to exercise are the subject of this report.

Clinical data The history was reviewed and a physical examination performed by at least two physicians Routine screening laboratory data was obtained. A standard 12 lead electrocardiogram and chest roentgenogram were obtained in all patients Three patients underwent a multistage bicycle stress test with a progressive increase in the workload until their heart rate reached 85 per cent of the age predicted maximum heart rate

Cardiac catheterization All patients underwent a standard right and left heart catheterization in the post absorptive state No patient was receiving digitalis Seconal sodium 100 mg was given intramuscularly one hour before catheterization Right heart pressures were obtained through a 7F Cournand catheter A 7F Eppendorf catheter was positioned in the left ventricle

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Society assumes a responsibility to its members by legislating for their protection, it is a responsibility of the scientific community to see that as far as possible this legislation is not done in a vacuum of ignorance

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Chest x ray	Electro cardiogram	Exercise test	Referring diagnosis
Normal	Non specific ST T changes PVCs	No ST changes abnormal blood pressure response	CAD‡
Normal	Non specific ST T changes	—	CAD vs pericardial disease
Old pleural thickening right side	IVCD lateral wall infarction		CAD with coronary insufficiency
Normal	Diffuse T inversion	—	CAD vs pericardial disease
Normal	WPW Type A†	—	CAD vs pericardial disease
Normal	LBBB PACs	—	CAD
Normal	Prior T inversion in III and aV$_F$		CAD
Normal	Normal	Normal	CAD
Normal	T inversion in II III aV$_F$	Normal	CAD vs myocarditis

atrial contr ction PVC = premature ventricular contra ti n

the increase in cardiac output in ml per minute per each 100 ml per minute increase of oxygen consumption All patients were subjected to supine exercise on a bicycle ergometer at workloads known to increase oxygen consumption two to threefold in normal subjects Left ventricular and pulmonary artery pressures were recorded at intervals of one minute for a total of 3 to 5 minutes Cardiac output was determined during the last minute of exercise Single plane left ventricular angiograms were performed in a 30 degree right anterior oblique projection using Renografin 76 Left ventricular pump function was assessed both by the visual impression of ventricular contraction and by calculation of ventricular volumes utilizing the method of Greene and colleagues[1] Coronary angiography was performed with the Sones technique

Results Clinical data (Table I)

History The subjects ages varied from 27 to 58 years (average age 41 4 years) and there were seven men and two women All patients suffered from recurrent chest pain over periods which varied from 1 to 60 months Only one subject (Case No 7) experienced typical angina pectoris, that is his central chest discomfort was definitely activity related, radiated into the right or left arm and was relieved by rest.*In all the remaining patients the chest pain was considered to be atypical of angina pectoris in that the pain never displayed a clear pattern of being induced by stress nor was it consistently relieved by rest or nitroglycerin Three patients (Nos 1 5 and 6) gave positive history of dyspnea on moderate exertion Two patients (Nos 1 and 4) had upper gastrointestinal abnormalities which could possibly have been the underlying cause of epigastric or lower mid chest discomfort. One patient (No 9) had had an upper respiratory infection three weeks prior to the start of the chest pain which suggested the possibility of myopericarditis as the cause of his discomfort

Physical examination None of the patients had a diastolic blood pressure greater than 90 mm Hg and none displayed abnormalities on precordial palpation Three patients showed a short Grade 1 2/6 ejection murmur in the aortic area. In one patient (No 4) a mid systolic click was detected intermittently No patient demonstrated clinical evidence of congestive heart failure and no abnormal filling sounds were heard.

*We are using the term typ cal angina pectoris as w s defined by the World Health Organization Expert Committee on Ca diovascular Dis e ses a d Hypertens on (1959) WHO Tech. Rep Ser 168 15

Table I Clinical data

Patient No	Age and sex	Chest pain			Dyspnea	Associated diseases	Blood pressure in mm. Hg	Cardiac murmurs
		Duration	*Recurrent*	*Typical**				
1	45M	22 mos	Yes	No	+	Sliding hiatus hernia	120/65	Systolic ejection murmur
2	34M	1 mo	Yes	No	–	–	130/70	–
3	37M	36 mos	Yes	No	–	Prior pneumonia emphysema	110/60	–
4	52F	1 mo	Yes	No	–	Duodenal ulcer	160/70	Systolic click and soft systolic ejection murmur
5	54M	–	Associated with episodes of tachycardia	No	+	Mild hypertension by history	170/85	–
6	37F	60 mos	Yes	No	+	–	120/75	Soft systolic ejection murmur
7	28M	9 mos	Yes	Yes	–	–	140/70	–
8	58M	36 mos	Yes	No	–	Partial thyroid ectomy in 1955	180/83	–
9	27M	1 mo	Yes	No	–	Recent upper respiratory infection	150/85	–

Typical refers to discomfort in the chest, arms or neck which was precipitated by activity and relieved by rest or nitroglycerin
†Patient had intermittent atrial fibrillation In the absence of WPW nonspecific ST T changes were present.
‡This diagnosis was usually suspected because of recurrent non pleuritic chest pain
Abbreviations CAD = coronary artery disease IVCD = intraventricular conduction disturbance LBBB = left bundle branch block PAC = premature
WPW = Wolff Parkinson White conduction abnormality

and pressures were measured with a Statham P23Db pressure transducer Intracardiac pressures and the first derivative of the left ventricular pressure (LV dp/dt) were recorded using a Sanborn Polybeam Recorder Zero reference pressure was at the mid chest level Cardiac output was determined by the Fick method in all but one patient in whom the indicator dilution method using indocyanine green was utilized. Exercise factor was calculated as

diastolic pressure in three subjects. Resting left ventricular end diastolic pressure (LVEDP) was clearly abnormal in only one patient. The first derivative of the left ventricular pressure was measured in seven patients and found to be normal; the resting cardiac and stroke indices were normal in all but one subject, and the angiographic stroke index was normal in the one subject (No. 1) whose cardiac output was not measured.

The exercise increase in cardiac output, as judged by the exercise factor, was normal in seven subjects in whom it was measured. Stroke index either increased or remained at the control level during exercise. However, the LVEDP rose to abnormal levels in all patients. The interrelationship of LVEDP and stroke index is shown in Fig. 5. The exercise pulmonary artery mean pressure also rose abnormally in relationship to

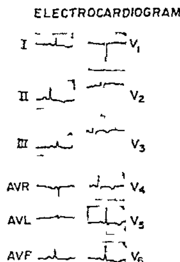


Fig. 2. Patient No. 4. This patient's electrocardiogram showed persistent nonspecific ST-T wave abnormalities.

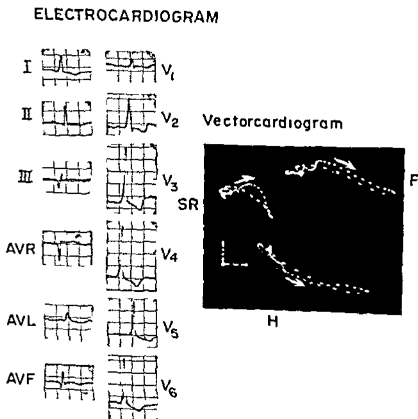


Fig. 3. Patient No. 5. The electrocardiogram shows a delta wave directed anteriorly, superiorly, and leftward, which is characteristic of Type A Wolff-Parkinson-White syndrome. An initial slowing of electrical forces is well seen in the vectorcardiogram.

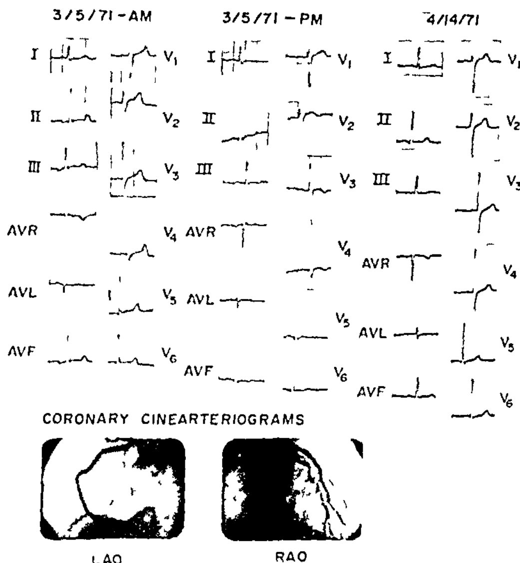


Fig 1 Patient No 2 These serial electrocardiograms illustrate transient ST T wave changes during one episode of severe substernal pain The first tracing taken during pain shows a junctional rhythm and ST segment straightening The middle record shows additional T wave abnormalities which occurred after the pain had sub sided The final record 5 weeks later is within normal limits Selected cineangiographic frames illustrate the patient s right coronary artery in the left oblique (*LAO*) view and the left coronary artery in a right oblique (*RAO*) view

Chest roentgenogram Chest films were nor mal in all patients except in subject No 3 who presented right pleural thickening

Electrocardiograms ST T segment abnor malities such as T wave inversion ST segment straightening or less than 1 mm ST segment depression, were seen in six patients (Figs 1 and 2) Complete left bundle branch block was pres ent in one patient Wolff Parkinson White syn drome, Type A, was seen in patient No 5 (Fig 3) The electrocardiogram of patient No 3 was con sistent with a posterolateral myocardial infarc tion (Fig 4) Only one patient (No 8) had an en tirely normal electrocardiogram Patient No 1 showed occasional premature ventricular beats patient No 6 had rare premature atrial beats and patient No 5 had had episodes of atrial fibrillation The bicycle stress test did not pro duce any significant ST changes in the three pa tients tested

Laboratory data There was no laboratory evi dence to suggest the presence of renal or hepatic disease Fasting blood sugar values ranged from 76 to 110 mg per cent A two hour postprandial sugar of 138 mg per cent was present in the sub ject with a fasting value of 110 mg per cent

Hemodynamic data (Table II)

Resting right heart pressures were normal, ex cept for mild increases in right ventricular end

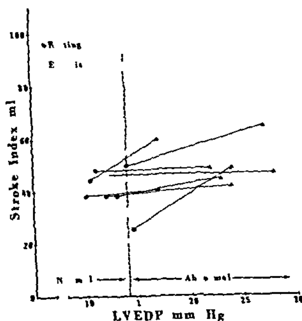


Fig 5 Relationship of left ventricular end diastolic pressure (LVEDP) and stroke index before and during mild physical exercise in 8 subjects. In all patients except one (patient No 1) resting LVEDP was normal (14 mm Hg) However exercise resulted in an abnormally high LVEDP in all the patients The exercise stroke index increased in three patients and was essentially unchanged in the remaining subjects

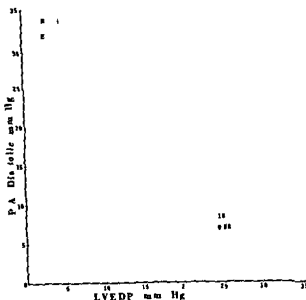


Fig 6 There is a positive correlation of left ventricular end diastolic pressure (*LVEDP*) with pulmonary artery (*PA*) diastolic pressure before and during mild physical exercise in 9 subjects

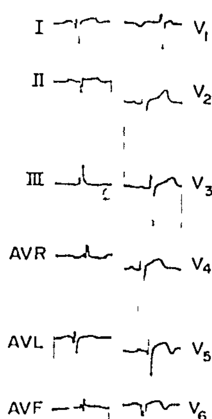
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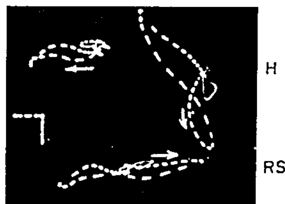
With the availability of selective coronary angiography it has become possible to assess the extent of coronary artery disease during life This important diagnostic tool has instructed us that frequently the clinical diagnosis of coronary artery disease is incorrect For example Proudfit and colleagues[2] have found that approximately 30 per cent of patients referred for coronary angiography because of suspected coronary artery disease have normal coronary arteriograms Many of these patients, who are free of obstructive coronary disease have experienced chest pain and/or display an abnormal electrocardiographic pattern other than that of myocardial infarction On the other hand, if the clinical diagnosis of coronary disease was based on a history of typical angina pectoris and/or electrocardiographic evidence of myocardial infarction obstructive coronary artery disease was found in the vast majority of such cases. The experience of Proudfit and associates then suggests that it is those patients with atypical chest pain who may or may not have obstructive coronary disease

However there is disagreement as to the prevalence of angina pectoris concomitant with normal coronary arteriograms Kemp and colleagues[3] have stated that 9 per cent of their patients undergoing coronary angiography have the anginal syndrome in the face of normal coronary arteriograms. In our experience 17 of 58 patients (30 per cent) who were thought to have chest pain secondary to coronary atherosclerosis had normal coronary arteriograms and normal resting intracardiac pressures However we wish to reiterate that only one of these 17 patients had typical angina pectoris a finding which emphasizes the infrequency of the problem of typical angina pectoris and normal coronary arteriograms

The causes of chest pain in patients with normal coronary arteriograms remain to be defined. Recently those patients with typical angina pectoris have received considerable attention[3-7] Some of these studies have demonstrated a myocardial ischemic response—i e lactate production by the myocardium during isoproterenol infusion and atrial pacing[3,8] Aberration of hemoglobin oxygen dissociation has been postulated as a cause of myocardial ischemia[9] but some workers have failed to find support for such

ELECTROCARDIOGRAM



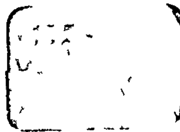


VECTORCARDIOGRAM



LAO





LAO RAO

CORONARY CINEARTERIOGRAMS

Fig 4 Patient No 3 This patient s unusual electrocardiogram shows sinus rhythm a mean frontal QRS axis of +165 degrees Q wave in leads I II aV_L V_5 and V_6 and a prominent R wave in V_2 These findings supported by the vectorcardiogram were interpreted as a posterolateral myocardial infarction and/or an intraventricular conduction abberation Selected right anterior oblique (*RAO*) and left anterior oblique (*LAO*) cineangiographic frames show an entirely normal dominant left coronary artery The normal right coronary is illustrated in an LAO view

the increase in cardiac output The exercise elevations in pulmonary artery diastolic pressure paralleled the changes in LVEDP (Fig 6)

Angiography (Table III)

All patients had a normal left ventricular end diastolic volume and a normal ejection fraction There were no areas of hypokinesia akinesia or dyskinesia of the left ventricle when viewed in the right anterior oblique projection Mitral re gurgitation was not present Coronary arteries and their sub branches were visualized in multi ple views and were found to be entirely free of even minor luminal irregularities

LV dp/dt (m. Hg/sec)	*CI* (L/min/M²)	*SI* (c c/M²)	*Exercise factor*	*A VO₂* (Vol. %)
1 750	–	–	–	5 1
–	–	–	–	–
–	2 8	46	–	4 37
–	5 3	46	764	8 46
1 717	2 6	44		4 55
–	5 9	69	1 047	7 34
?400	1.8	25		5.22
–	4 8	48	1 015	8 16
2 075	3 0	49		4 0[illegible]
–	5 7	64	803	8 17
1 075	3 2	38		3 22
–	5 2	41	610	6 75
1 412	2 3	38		4 69
–	4 4	44	832	8 19
–	2 7	47		4 57
–	4 4	48	648	8 62
1 575	2 2	38		–
–	3 5	40	–	–
1 714	2 6	41		4 47
±163	±0 2	±2 7		±0 22
	4 9	49	845	7 96
	±0 3	±3 0	±53	±0 25
–	<0 001	0 07	–	<0 001

reflect ventricular function [10,12] Overt heart failure is associated with elevated end diastolic pressures. Furthermore the response of left ventricular end diastolic pressure to stress has been described by Ross and colleagues[12] and by Gorlin and associates[13] who have shown that the normal response to physical exercise is an increase in cardiac output, mediated primarily by tachycardia and augmented cardiac contractility that in the supine position stroke volume changes very little and that the LVEDP rises no more than 2 mm Hg or actually falls from the resting value An abnormal ventricle limited by diminished diastolic compliance and decreased catecholamine augmentation of contractility may increase its end diastolic volume when faced with an increased venous return during exercise With a stiffer ventricle an abnormally high filling pressure (LVEDP) will result.

Our patients showed a marked increase in LVEDP in response to mild supine exercise This illustrates that an altered left ventricular compliance may exist in the presence of a normal ventriculogram and normal resting intracardiac pressures The degree of left ventricular dysfunction was minimal since pump function—as reflected by the exercise factor exercise stroke index and left ventricular ejection fraction—was normal. The measurement of LVEDP during supine exercise proved to be a more useful index than either the ejection fraction of LVdp/dt in the recognition of minimal cardiac dysfunction This observed abnormality of left ventricular function is not specific for any one cardiac disorder Similar hemodynamic alterations have been found in coronary artery disease [5] in patients with typical angina pectoris and normal coronary arteries [5] and primary myocardial disease including idiopathic left ventricular hypertrophy [11]

In our group of patients with chest pain and normal coronary arteriograms the detection of minimal left ventricular dysfunction implies that quite possibly the chest pain was secondary to a cardiac disorder In addition our patients had a high incidence of electrocardiographic abnormalities of a type which as a rule do not permit one to arrive at an unequivocal diagnosis of heart disease but certainly raise that possibility

Although latent idiopathic hypertrophic subaortic stenosis was not specifically excluded during isoproterenol infusion our patients lacked the usual features such as a variable systolic ejection murmur an atrial sound and electrocardiographic evidence of left ventricular hypertrophy Our subjects did share many of the features usually associated with primary myocardial disease [14-16] Chest pain arrhythmias dyspnea and electrocardiographic abnormalities are common in all type of cardiomyopathy and myocarditis. Until more specific causes of chest pain can be defined, it would seem appropriate to continue to consider these patients as belonging to the over all group of cardiomyopathies

Not uncommonly patients with coronary artery disease present symptoms similar to those manifest in our study group We believe that at the present time coronary angiography is the only means of identifying with any degree of certainty patients who do not have large vessel coronary artery disease as the cause of their chest pain Furthermore the study emphasizes that patients with recurrent chest pain of probable

Table II Individual hemodynamic data

Patient no	Condition	Work load in ft/lbs	Heart rate	RA (mm. Hg)	RV (mm. Hg)	PA (mm. Hg)	PAm (mm. Hg)	PW (mm. Hg)	LVSP (mm. Hg)	LVEDP (mm. Hg)
1	Rest		50	6	29/9	25/13	16	9	120	17
	Exercise	1 100	90	–	–	48/18	24	–	–	28
2	Rest		60	9	30/11	25/13	18	15	110	12
	Exercise	1 600	96	–	–	45/22	34	–	–	28
3	Rest		60	4 5	–	29/12	18	13	105	10 5
	Exercise	1 100	100	–	–	41/19	26	–	–	17
4	Rest		70	4	27/6	29/12	19	12	165	14 5
	Exercise	710	100	–	–	49/17	31	–	185	24
5	Rest		60	5	30/4	30/12	18	–	165	14
	Exercise	1 100	100	–	–	–	28	–	190	27
6	Rest		83	5	–	21/10	15	8	150	12
	Fxercise	710	120	–	–	35/24	28	–	163	24
7	Rest		60	4	33/9	27/12	16	13	115	13
	Exercise	1 100	100	–	–	47/18	29	–	118	23
8	Rest		58	5	25/6	26/8	16	9	162	11
	Exercise	1 100	90	–	–	45/20	28	–	–	2?
9	Rest		58	4	–	23/7	12	9	130	10
	Exercise	1 600	88	–	–	32/14	20	–	150	17
Mean	Rest		62	5 1			16	11	136	13
	SEM		±3 1	±0 4			±0 7	±0 9	±8	±0 7
values	Exercise		98	–			28		161	23
	SEM		±3 2	–			±1 3		±13	±1 4
P Value										
Rest vs	Exercise		<0 001	–			<0 001		0 1	<0 001

an abnormality in similar subjects[3,6] Other entities which could produce typical angina pectoris in the face of normal coronary arteriograms, are small vessel coronary disease microcirculatory disturbances and undetected idiopathic hypertrophic subaortic stenosis

We wish to focus attention on the more common problem of those patients with normal coronary arteriograms and recurrent chest pain not typical of angina pectoris A comparison of our patients with other reported series of patients with angina pectoris and normal coronary arteriograms emphasizes some major differences Only two of our subjects were female whereas females are predominant in other series[3,6] and Likoff and colleagues[4] subjects were exclusively premenopausal women Intraventricular conduction disturbances and arrhythmias were rare in other reports Our nine subjects were identified by their abnormal hemodynamic response to exercise, whereas eight subjects exercised by Likoff and colleagues[4] had a normal response However, Dwyer and associates[5] did find similar abnormal exercise hemodynamics in their patients Thirty four per cent of patients studied by Kemp and colleagues[3] had abnormalities of glucose tolerance, but in our patients as well as in those described by Likoff and associates[4] diabetes mellitus was uncommon In agreement with the other reports our patients did not have associated systemic disorders which could cause small vessel disease

The above diversity of clinical features highlights the fact that recurrent chest pain can be the predominant symptom in multiple cardiac disorders Whereas typical angina pectoris in the absence of other known causes has a high specificity for coronary artery disease this correlation is not present when the pain is not characteristic of angina pectoris It remains therefore of paramount importance to accurately describe a recurrent chest pain

The ventricular end diastolic pressure at rest and under an imposed stress has been thought to

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Table III Angiographic data

Patient no	EDV in cc/M²	ESV in cc/M²	EF	Akinesia dyskinesia	Coronary arteriography
1	49 0	4 9	0 90	–	Normal
2	54 2	14 3	0 73	–	Normal
3	91 4	27 8	0 69	LV wall hypertrophied	Normal
4	44 5	5 8	0 87	–	Normal
5	62 5	10 8	0 83	–	Normal
6	61 0	6 2	0 89	–	Normal
7	68 0	18 2	0 73	–	Normal
8	–	–	–	–	Normal
9	79 7	18 4	0 77	–	Normal
Mean ± SEM	63 8±5 6	13 3±2 8	0 80±0 03		

cardiac origin may fail to demonstrate any hemo dynamic abnormality in the resting state Pa tients referred to a cardiac catheterization laboratory for investigation of chest pain should in addition to resting observations undergo some other additional evaluation of left ventricular function

Summary

During the past year the response to supine exercise was included in the hemodynamic evaluation of almost all patients referred to our laboratory because of chest pain Seventeen of 58 patients with chest pain were found to have nor mal coronary arteriograms normal resting in tracardiac pressures and a normal left ventriculogram Nine of these 17 patients had an abnormal exercise response as evidenced by a significant increase in the left ventricular end diastolic pressure The degree of left ventricular dysfunction was minimal since exercise cardiac output increased normally stroke volume was maintained during exercise and the calculated left ventricular end diastolic volumes and ejec tion fractions were normal Atypical chest pain was present in all but one subject who had typi cal angina pectoris In addition, the group shared features such as arrhythmias dyspnea and non specific electrocardiographic abnormalities which are common to all forms of cardiomyopa thy We suggest that this patient group may fre quently be mislabeled as having no cardiac dis order when no further evaluation of cardiac function, other than resting intracardiac pressures and a left ventriculogram is carried out

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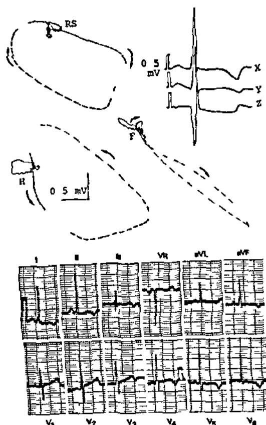


Fig 1 Scalar X, Y Z leads planar VCG and 12 lead ECG of Case 2 a girl 14 years old The spatial QRS loop has a smooth contour but is abnormally large in magnitude The initial vectors are displaced leftward, anteriorly and inferiorly The T loop is abnormally oriented to the right anteriorly and superiorly The beam is interrupted at intervals of 1 msec The ECG tracing is indicative of left ventricular hypertrophy with inversion of the T wave

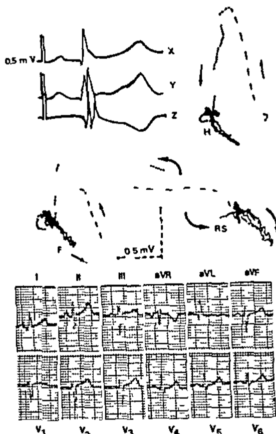


Fig 2. Frank X, Y Z leads and VCG and ECG tracings of Case No 4 a man 33 years old. The QRS loop shows prominent posteriorly directed forces with several notches in the contour The right sagittal plan shows a double figure 8 initially clockwise Dash intervals of 1 msec

Lead Z, Q wave duration in Lead Z Q and R amplitudes in Lead X, and R wave amplitude in Leads Y and Z The direction of inscription of the vector loops was studied as well as the maximum QRS vector of the horizontal plane loop

Results

The results are summarized in Tables I and II

The P R interval varied from 0 12 to 0 16 sec The QRS duration ranged from 0 075 to 0 100 sec The Q T interval ranged from 0 32 to 0 42 sec only patient No 2 having an abnormal Q T value The heart rate ranged from 65 to 103 beats per minute The AQRS was within normal limits varying from −30 to +60 degrees The AT was frankly abnormal in patient No 2 being situated at +200 degrees in this subject the T waves were negative in the precordial leads from V_2 to V_6

The scalar tracings with the Frank system showed Q wave amplitude in Lead Z ranging from 0 15 to 1 40 mv only one patient having an abnormally large Q wave amplitude R wave amplitude in Lead Z averaged 0 89 mv (range 0 35 to 1 55 mv) none being abnormally large or abnormally small The average Q/R amplitude ratio in Lead Z was 0 561 ranging from 0 157 to 1 866 one being below and one exceeding the normal ratio (0 38 to 1 43) The Q duration in Lead Z ranged from 0 015 to 0 040 sec (normal 0 020 to 0 048 sec) the Q amplitude in Lead X was 0 in three patients and ranged from 0 010 to 0 350 mv in the other seven The R wave in Lead X was abnormally small in one (patient No 5) and abnormally large in three (patients No 2 6 and 7) the values ranged from 0 20 to 2 80 mv

The vectorcardiogram in Friedreich's ataxia

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Several studies have been devoted to Friedreich's ataxia a heredofamilial disorder which have put in evidence the association of neurological impairment and of cardiac damage The cardiac alterations since described consist in muscle fiber hypertrophy interstitial fibrosis focal degeneration of muscle fibers and rarely, active necrosis[1 3] Rare cases of coronary arteriopathy and of non obstructive cardiomyopathy have been reported[4]

Left ventricular hypertrophy and inversion of T waves are the most common electrocardiographic pattern observed in patients with Friedreich s ataxia less conspicuous ECG changes are right axis deviation and abnormal rotation of the heart These electrocardiographic abnormalities have been considered to reflect dystrophic lesions in the myocardium[5] or to represent a genetically determined alteration and have been observed in a large proportion of cases In order to perform a more detailed analysis on these alterations a vectorcardiographic study was performed in ten young subjects with Friedreich s ataxia

Methods

The patients studied were hospitalized in the Neurological Hospital of the University of Milan and were sent to our Department for cardiac investigation All were unequivocally affected by Friedreich s ataxia according to rigid neurological criteria including the development of progressive ataxia without remission during childhood or adolescence The plantar responses were extensor the tendon reflexes were diminished or absent, and there was postural and vibratory loss in the legs Two had pes cavus two had nystagmus and strabismus None had kyphoscoliosis In all cases a muscular biopsy was concordant with the diagnosis of Friedreich s ataxia

The mean age was 18 years ranging from 13 to 33 Cases 1, 2, and 3 were sisters aged 17, 14 and 13 years respectively whose initial symptoms appeared 5 3 and 2 years before our study Case 4 was a man 33 years old whose symptoms began at age 7 apparently after a car accident Cases 6 and 7 were brothers 24 and 20 years old respectively Case 5 a 21 year old man, had a progression of the neurological disease that was slower than usual his lurching gait initiated at age 7 and his walking ability was lost at age 20

An apical systolic murmur was present in two cases There was no complaint of edema or dyspnea A resting tachycardia was present in two patients (Cases 5 and 9) but frequent episodes of paroxysmal tachycardia were reported by most of them One patient (Case 2) complained of repeated attacks of precordial pain No cardiac arrhythmias were recorded

Vectorcardiographic tracings were recorded by the Frank system[6] using the Hewlett Packard 1520 A model with a 197 A model camera The electrodes were placed in the fourth intercostal space as recommended for the supine position[7] The three orthogonal scalar leads X Y, and Z were simultaneously recorded and frontal right sagittal and horizontal loops were inscribed The beam was interrupted each 1 or 2 5 msec

Scalar tracings were analyzed for P R interval QRS duration Q T interval heart rate Q and R amplitudes in Lead Z Q/R amplitude ratio in

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Q_Z amplitude (mv)	*R_Z amplitude (mv)*	*Q/R_Z*	*Q dur z (sec.)*	*Q_X amplitude (mv)*	*R_X amplitude (mv)*	*R_Y amplitude (mv)*
0 20	0 55	0 363	0 025	no Q wave	1 15	1 05
1 40	0 75	1 866	0 040	no Q wave	2 15	1 45
0 30	0 35	0 857	0 030	no Q wave	0 80	1 15
0 25	1 00	0 250	0 015	0 100	0 60	0 45
0 40	0 70	0 571	0 030	0 025	0 20	0 50
0 35	1 00	0 350	0 030	0 225	2 50	0 55
0 65	1 55	0 419	0 035	0 350	2 40	0 85
0 35	1 25	0 280	0 030	0 020	2 15	0 80
0 15	0 95	0 157	0 025	0.010	0 85	1 25
0 40	0 80	0 500	0 030	0 150	2 80	0 90

Friedreich s ataxia

Maximum T vector			*QRS rotation*		
Frontal (Direction)	*Right sagittal (Direction)*	*Horizontal (Direction)*	*Frontal*	*Right sagittal*	*Horizontal*
46	102	120	CCW	CW	CCW
206	26	155	figure of 8 CCW	CW	CCW
62	99	9	CCW	CW	CCW
46	41	48	CCW	figure of double 8 CW	CCW
82	47	88	CCW	CW	CCW
72	0	46	figure of 8 CCW	CW	CCW
29	6	76	figure of 8 CCW	CW	CCW
60	90	25	figure of 8 CCW	CW	CCW
24	80	15	CW	CW	CCW
34	15	35	figure of 8 CCW	CW	CCW

3) The irregularities involved either the QRS loops as the T loops and were particularly evident in the sagittal and in the frontal planes Cases 1 2 and 3 were sisters with a different degree of nervous impairment Their vectorcardiographic patterns were quite similar and consisted in an augmentation of QRS vector amplitude without irregularities of the loop contour (Fig 1) The cardiac involvement was greatest in patient No 2 who had more severe neurological signs and was relatively minor in patients No 1 and 3 whose nervous symptomatology was proportionally smaller Similar observations were made in patients No 6 and 7 two brothers with different degree of neurological impairment, where the vectorcardiographic involvement was proportional to the degree of nervous damage

Discussion

Friedreich s disease is a heredofamilial disorder whose chief clinical manifestation is ataxia secondary to degeneration of the spinocerebellar tracts although the posterior columns and corticospinal tracts are also involved Some skeletal deformities of the thorax commonly develop which may simulate or obscure signs of heart dis

Table I Summary of results of vectorcardiographic study in 10 youthful subjects with Friedreich s ataxia

Patient no and initials		Sex	Age (yr)	Onset of symptoms	HR*	PR (sec)	QRS (sec)	QT (sec)
1	M C	F	17	12	83	0 12	0 085	0 36
2	L C	F	14	11	75	0 14	0 090	0 42
3	R C	F	13	11	75	0 14	0 080	0 38
4	S P	M	33	7	79	0 12	0 080	0 36
5	A M	M	21	3	103	0 14	0 080	0 32
6	M G	M	24	20	75	0 14	0 080	0 40
7	G G	M	20	18	78	0 14	0 080	0 38
8	M M	F	10	8	75	0 14	0 075	0.34
9	C M	F	16	14	100	0 12	0 075	0 32
10	R A	M	18	16	65	0 16	0 100	0 38

HR = heart rate

Table II Direction and magnitude of QRS and T vectors and rotation of QRS in 10 patients with

Patient no	Sex	Maximum QRS vector					
		Frontal		Right sagittal		Horizontal	
		Direction	Magnitude (mv)	Direction	Magnitude (mv)	Direction	Magnitude (mv)
1	F	50	1 550	104	1 250	10	1 025
2	F	32	2 625	55	1 725	27	2 250
3	F	49	1 375	90	1 025	15*	0 850
4	M	40	0 650	237	1 175	284	1 100
5	M	66*	0 450	214	0 800	270	0 675
6	M	10	2 400	176	1 100	354	2 400
7	M	12	2 250	171*	1 575	19	2 225
8	F	20	2 250	180	1 250	355	2 250
9	F	52	1 450	114	1 375	325	1 000
10	M	12	2 750	107	1 750	352	2 750

Abbreviations CCW = counterclockwise CW = clockwise

The R wave in Lead Y ranged from 0 45 to 1 45 mv , three being abnormally small (patients No 4, 5, and 6)

In the frontal plane the loops were clockwise in one, counterclockwise in four and in a figure of 8 pattern which was predominantly counterclockwise in five (Figs 1 2 and 3) In the right sagittal plane the loops were clockwise in nine and in a figure of 8, predominantly clockwise, in one In the horizontal plane, all the ten loops were counterclockwise The maximum QRS vector ranged from 270 to 27 degrees in the horizontal plane and from 10 to 66 degrees in the frontal plane

The maximum QRS vector magnitude ranged from 0 67 to 2 75 mv in the horizontal plane (normal values 0 85 to 1 95 mv) being abnormally small in one (patient No 5) and abnormally large in five (patients No 2 6 7 8 and 10) In the frontal plane the maximum QRS vector magnitude ranged from 0 45 to 2 75 mv (normal values 0 90 to 2 20 mv) being abnormally small in two (patients No 4 and 5) and abnormally large in four (patients No 2 6 8 and 10)

The vectorcardiographic loops presented regular contours in three patients (Fig 1) and were highly irregular in contour in seven (Figs 2 and

mally small in three In all five subjects the QRS loops were grossly irregular and showed several indentations of the contour and continuous abnormalities in the direction of inscription These aspects were present in the three orthogonal planes particularly in the right sagittal plane (Figs. 2 and 3) Such diffuse irregularities are suggestive of focal myocardial lesions and are consistent with the pathological findings of diffuse focal degeneration of muscle fibers or of focal necrosis, as previously reported [3]

It is worth noting that the vectorcardiographic abnormalities observed in three sisters of the present group were strictly similar and appeared closely parallel to the degree of their nervous impairment. Such observations strengthen the hypothesis that the cardiac involvement in Friedreich's ataxia develops progressively and runs a course parallel to that of the neurological alterations

Summary

A Frank system vectorcardiographic analysis has been performed in 10 patients with Friedreich's ataxia None had clinical signs of heart failure nor kyphoscoliosis The electrocardiographic patterns were abnormal in five patients showing signs of left ventricular hypertrophy with inversion of T waves and abnormal rotation of the heart axis and appeared practically normal in the other five On the contrary the vectorcardiographic features were abnormal in all ten patients studied A prominence of lateral forces was present in the VCG of the first group in accordance with the scalar ECG while patterns suggestive of diffuse myocardial damage were observed in the patients with a normal electrocardiogram The vectorcardiographic alterations appeared strictly parallel to the degree of nervous involvement this was particularly evident in three sisters and in two brothers whose vectorcardiographic abnormalities were similar in type and were proportional to the degree of neurological impairment

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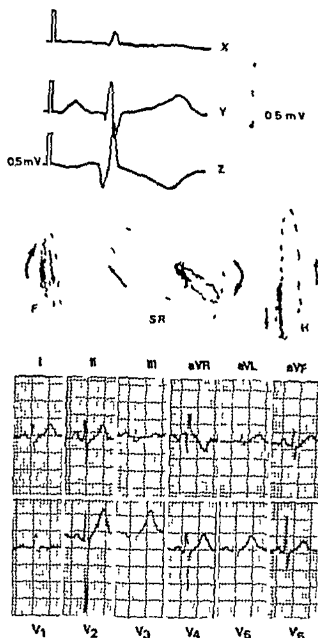


Fig 3 *Case No 5* a 21 year old man Notches and indentations of the contour are evident in the loops of the *frontal* and right sagittal planes The electrical forces are predominantly oriented backward. *The beam is interrupted at intervals of 2.5 msec The standard 12 lead ECG is normal*

ease The association of Friedreich s ataxia with cardiac disease was clearly established since *1929 when Mollaret[8] first reported the* presence of electrocardiographic abnormalities Successively a high incidence of heart involvement was demonstrated it consists in muscle fiber hypertrophy, interstitial fibrosis focal degeneration of muscle fibers, and rarely active necrosis[3] Obliterative disease of small intramural coronary arteries has been described though only rare cases of angina pectoris have been reported[5,9] Heart failure occurs in a high percentage of patients with Friedreich's ataxia[4] The onset of the cardiac symptoms and their severity are extremely variable usually they develop long after the neurologic disorder is manifest *Hemodynamic* studies have demonstrated moderate degree of ventricular dysfunction[10] Recently two cases of Friedreich s ataxia associated with idiopathic hypertrophic subaortic stenosis have been reported[4]

Electrocardiographic abnormalities have been observed in a large portion of cases even in young children, close to the onset of the neurological symptoms and signs Left ventricular hypertrophy, dominated by inversion of T waves in Leads I II aV$_F$ and V$_{5,7}$ was the most common picture[10,12] Some other patients on the contrary showed less conspicuous ECG changes, which consisted in right axis deviation or abnormal rotation of the heart[9] As for other neuropathic diseases associated with cardiomyopathy these electrocardiographic abnormalities have been considered to reflect dystrophic lesions in the myocardium[5] or to represent a genetically determined alteration

In the present study we utilized the Frank VCG system in ten patients with Friedreich s ataxia to obtain *more descriptive information* on planar loops and scalar displays of X Y, and Z orthogonal leads The vectorcardiographic analysis offered a useful supplement to the standard scalar ECG and permitted us to gain rigid quantitative standards useful to the analysis of tracings and to an insight into the mechanisms responsible for the distinctive pattern *In the* present study the QRS in the standard ECG was classified as abnormal in five subjects being suggestive of left ventricular hypertrophy and appeared to be normal in the remaining five On the contrary at the vectorcardiographic analysis the QRS pattern was abnormal in all ten patients. Abnormally prominent lateral forces were present in five of them and were represented by an abnormally small ratio Q/R in Lead Z and abnormally large R waves in Lead X an abnormally large Q wave in Lead Z with an augmented Q/R ratio in the same lead was observed in one (Fig 1) These observations are concordant with the information derived from scalar ECG's In the remaining five subjects with apparently normal conventional ECG's, the vectorcardiographic aspects were indicative of diffuse myocardial damage A Q wave in Lead X was absent in three an R wave in Lead Y was abnor

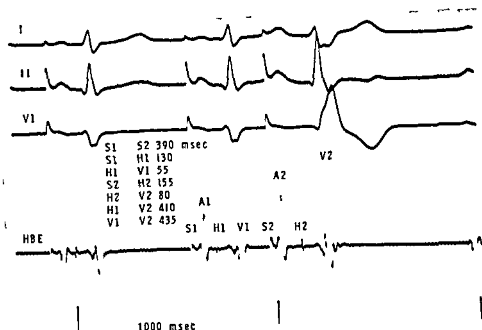


Fig 1 Effect of atrial pacing with a fixed cycle length on A V conduction. *Top panel*, ECG Leads I II and V_1 are shown with the His electrogram during atrial pacing by stimulus (S) which is conducted to the atrium (A) His potential (H) and ventricle (V) The pacing rate is 130 beats per minute One to-one conduction between the stimulus atrium His potential and ventricles *Bottom panel* The pacing rate has been increased to 140 beats per minute Atrioventricular block is now present with alternate stimuli being blocked between the atrium and His bundle The pacing rate where A V block develops is called the Wenckebach point (WP) in Fig 4 and the text This illustration is similar to those previously reported

was defined as the latest atrial test response which fails to conduct to the His bundle [5] The functional refractory period of the AV node was defined as the minimum interval between two successive His bundle responses both propagated from the atrium [5] Following determination of the refractory periods the atria were paced using a single stimulus with a fixed cycle length until AV Wenckebach occurred as shown in Fig 2 [6]

Coronary arteriograms were performed in all patients by the Sones [7] or Judkins [8] technique The patients were then divided into two groups on the basis of a right coronary artery score according to the method of Friesinger Page and Ross [9] by two independent observers In this system the following values were assigned 0 = no arteriographic abnormalities seen 1 = trivial irregularities in luminal diameter 2 = localized narrowing estimated to be greater than 50 per cent but less than 90 per cent of luminal cross sectional area 3 = multiple narrowing in the same vessel estimated to be greater than 50 per cent and less than 90 per cent 4 = narrowing(s) estimated to be greater than 90 per cent of luminal cross section area and 5 = total obstruction of a vessel without any filling of the distal segment from the proximal portion Patients having a right coronary artery which supplied the inferior surface of the heart and right coronary artery scores of 0 to 1 were considered not to have significant right coronary artery disease and were placed in the control group Patients having over 50 per cent lesions in the right coronary artery i e scores between 2 and 5 were placed in the group called right coronary artery disease

The presence or absence of left coronary artery disease was not used as criteria for selection Of the patients reported, only four were seen by one of the authors at the onset of acute myocardial infarction Thirty six patients were seen initially at other hospitals In these patients the records available were not sufficient to evaluate all objective parameters of myocardial infarction such as enzyme elevation and changes in body temperature or sedimentation rate For the purpose of this study a previous myocardial infarction was diagnosed on the basis of a typical history plus electrocardiographic changes consistent [10] with infarction When available a review of hospital records was made to search for previous atrioventricular conduction disturbances

Latent defects of atrioventricular conduction in right coronary artery disease

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The occurrence of heart block during inferior myocardial infarction has been attributed to ischemic impairment of atrioventricular conduc tion With the introduction of His bundle record ings, the site of block has been localized to the area of the atrioventricular node [1] Since the ar terial supply to this area is derived from the right coronary artery in 80 to 90 percent of the cases atherosclerosis of this vessel is the prin cipal cause [2] Although the electrocardiographic features have been largely reversible [3,4] the oc currence of latent abnormalities in AV conduc tion either prior to or following inferior myocar dial infarction has not been investigated The purpose of this study was to compare the func tional properties of the atrioventricular conduct ing system in patients with and without signifi cant disease of the right coronary artery

Materials and methods

AV conduction was studied in 40 patients un dergoing catheterization for investigation of chest pain who met the following criteria. (1) no patient had sustained a documented myocardial infarction during the six months prior to study (2) the patients were receiving no drugs known to affect AV con duction, (3) the patients had resting heart rates of 85 beats per minute (BPM) or less and (4) the patients had normal intervals on the His bundle electrogram including P H times between 80 to 140 msec. H V times between 30 to 55 msec and had no intraventricular conduction defect No patient had significant valvular heart disease In each case the posterior descending coronary artery was seen to arise from the right coronary ar tery Patients in whom the posterior descending artery arose from the circumflex vessel were ex cluded.

All patients were studied in the resting post ab sorptive state without sedation

Evaluation of the AV conducting system was ac complished by two methods The effective and functional refractory periods of the AV node were determined by the extra stimulus method as shown in Fig 1 [5] With the atria driven at a rate of 80 to 85 BPM, a premature atrial impulse was introduced at progressively shorter intervals of 10 msec The stimulus following the premature beat was in hibited by a relay circuit to facilitate measurement. The His bundle electrogram was obtained by posi tioning a bi or tri polar catheter in the area of the tricuspid valve The atria were paced by a Tektronix 2600 series stimulator connected to a battery powered stimulus isolation box which delivered a stimulus 2 msec in duration at twice the diastolic threshold All measurements were made on an Electronics for Medicine recorder at paper speeds of 100 to 200 mm per second

The effective refractory period of the AV node

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because of the onset of the atrial relative refractory period at short coupling intervals[11] Since the nodal effective refractory period could not be measured in six patients in the control group and two patients in the group with right coronary obstruction this measurement was not compared in the two groups

There was poor correlation of the results of conduction studies with the left or total coronary artery score the duration of symptoms and the presence of collaterals

Seventeen patients in the right coronary artery disease group were thought to have had a previous myocardial infarction on the basis of clinical history and electrocardiographic changes Fifteen of these patients had diagnostic electrocardiographic changes at the time of study Twelve patients had inferior infarctions Two had anterior infarctions only and one patient had both anterior and inferior infarctions In two cases, ECG changes during hospitalization were consistent with subendocardial infarction[10] Only four patients were hospitalized at the author s primary hospital during the acute stage of infarction none of these patients had AV conduction disturbances during the acute stage In each case more than six months had elapsed from the time of the infarction to the time of study Five patients had no clinical or electrocardiographic evidence of infarction No difference was obtained between the results of conduction studies in the 17 patients with and five patients without a history of myocardial infarction

Discussion

Atrioventricular block has been observed clinically in approximately 20 per cent of patients with acute inferior infarction[4,12,14] The conduction defect is usually gradual in onset, often with progression from first degree block to Wenckebach periods to complete AV block The usual clinical observation of a normal QRS duration has been confirmed by specialized conduction studies demonstrating prolongation of mainly the P H time indicating conduction delay in the region of the AV node[15] Although the conduction disturbance most often appears to be reversible functional impairment in AV conduction for periods of several days has been indicated after inferior infarction[16] Postmortem studies of the AV conduction system following fatal inferior infarction have suggested that

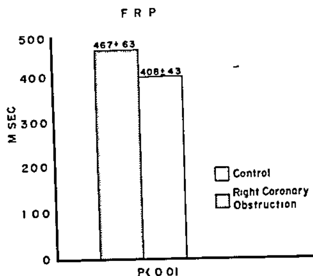


Fig 3 Results of functional refractory period measurements (msec) The functional refractory period of the AV node in patients with coronary artery disease was found to be significantly longer (P<0 01) than determinations in patients in control group

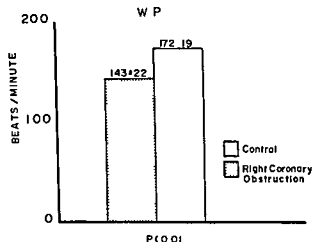


Fig 4 Results of atrial pacing with fixed cycle length Measurement of the rate in beats per minute where atrio ventricular block or Wenckebach (*WP*) developed during atrial pacing Patients in the control group could maintain higher (P<0 01) paced rates before development of atrioventricular block.

ischemia rather than frank infarction of the AV nodal tissues is responsible for the conduction disturbances[17]

This study was designed to test the hypothesis that AV conduction defects might exist in a chronic form following the development of right coronary artery disease The results demonstrate a significant difference between the group of pa

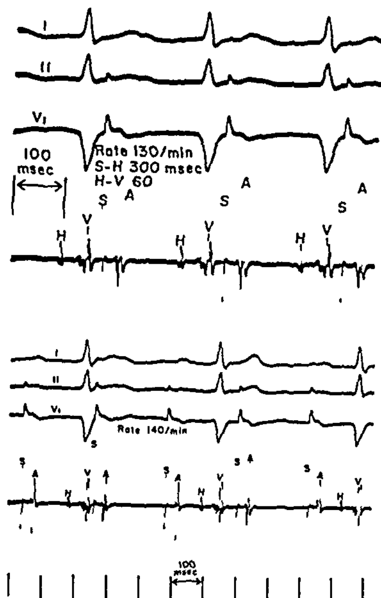


Fig 2 Effect of premature atrial stimulation using coupled atrial pacing ECG Leads I II and V_1 are shown with the His electrogram (HBE) With the atria (A_1) driven at a basic rate between 80 to 85 beats per minute by the stimulus (S_1) a premature stimulus (S_2) is introduced every eighth to tenth beat and subsequent stimuli inhibited to facilitate measurement The S_1 S_2 interval is reduced in increments of 5 to 10 msec and the conduction intervals measured as shown In this instance aberrant conduction of the premature beat develops at an interval between His potentials of 410 msec (H_1 H_2 interval) Measurement of the H_1 H_2 interval allows assessment of the functional refractory period (FRP) of the AV node even in the presence of block below the His bundle The FRP of the AV node is the minimum H_1 H_2 interval with both His spikes conducted from the atria *A* = atria *H* = His *V* = ventricular depolarization

Results

Eighteen patients with an average age of 46 ± 6 (SD) years were found to have either less than 50 per cent occlusion of the right coronary artery (six patients) or no coronary lesions (12 patients) Two patients in this group had over 50 per cent narrowing of the left anterior descending coronary artery Baseline conduction studies in this group with a resting heart rate of 76 ± 6 BPM included a mean P H time of 101 ± 31 msec and mean H V time of 46 ± 9 msec

Twenty two patients with an average age of 50 ± 8 years were found to have greater than 50 per cent occlusion of the right coronary artery The mean duration of symptoms in this group was 31 ± 22 months and ranged from eleven months to six years The mean age in this group was 50 ± 8 years Twelve patients had complete occlusion six patients had over 90 per cent occlusion one patient had multiple areas of 50 per cent narrowing and three patients had single areas of over 50 per cent narrowing The mean right coronary score was 4 2 ± 1 The mean coronary score for the left anterior descending was 3 0 ± 1 7 and for the circumflex was 2 5 ± 1 7

Eleven patients had collateral circulation from the left coronary artery to the right six patients had collaterals from the proximal to the distal right coronary artery Six patients had collateral filling of the left anterior descending or diagonal from the right coronary artery Baseline conduction studies in this right coronary artery disease group with a mean heart rate of 68 ± 11 BPM showed a longer resting P H time of 122 ± 19 msec ($P<0\ 05$) and a similar H V time of 49 ± 10 msec

Results of the conduction studies are shown in Figs 3 and 4 For the control group the mean functional refractory period (Fig 3) was 408 ± 43 msec, with a range of 340 to 490 msec and a median value of 407 msec In patients with significant right coronary artery disease the mean functional refractory period was 467 ± 63 msec. ($P<0\ 01$) with a range of 400 to 565 msec and a median value of 458 msec The values obtained for the onset of AV Wenckebach (Fig 4) were 172 ± 19 beats per minute for the control group with a range of 140 to 200 beats per minute and a median value of 170 beats per minute In the right coronary artery disease group the mean value for the onset of AV Wenckebach was 143 ± 22 beats per minute ($P<0\ 01$) with a range of 90 to 200 beats per minute and a median value of 140 beats per minute

After the beginning of the study, it became apparent that the AV nodal effective refractory period could not be determined in all instances

and earlier development of atrioventricular Wenckebach during rapid atrial pacing (143 ± 22 BPM in the coronary obstruction group versus 172 ± 19 BPM in the control group P<0 01) in patients with significant disease of the right coronary artery when compared to the control group Although all patients were found to have resting intervals on the His bundle electrogram within normal limits the group with right coronary obstruction had slightly longer values for the resting P H interval (122 ± 19 msec versus 101 ± 31 msec in the control group P<0 05) This study establishes that latent defects in atrioventricular conduction exist in patients with significant disease of the right coronary artery in the absence of acute infarction

The authors appreciate the clerical skills of Miss Lisa Goodwin and the technical assistance of Miss Joyce Sherwood and Miss Jacquelyn Gammill

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tients having severe right coronary artery obstruction and those with insignificant arterial disease Although the numbers of patients are small, the presence or absence of electrocardiographic changes consistent with previous infarction was not associated with differences in the conduction studies

The explanation for the altered AV conduction in patients with right coronary obstruction requires further investigation Although the results may be due to actual ischemia of the AV node, this assumption has not been proved. Measurements of coronary blood flow in patients with and without obstructive disease have yielded conflicting results The majority of reports appear to show no decrease in resting coronary flow even in patients with angiographically proved coronary artery disease [18-21] In this study when the results of conduction studies were compared with the presence or absence of collateral circulation no correlation was found It is apparent that collateral circulation does not insure normal AV conduction in patients with right coronary disease In a similar manner it has been shown that collateral circulation does not protect against the development of ischemic ST changes during stress testing for angina [22]

Clinical observations have demonstrated the frequent occurrence of sinus bradycardia and other symptoms resembling vasovagal reactions in inferior infarction [23] These symptoms often respond to atropine [24] It is possible that alterations of the right coronary artery may alter the sensitivity of the AV conducting system to autonomic influences Additional studies are needed to confirm or deny this possibility

A comparison of values obtained in these patients with those previously reported is of interest Two reports of determination of the paced rate at which AV Wenckebach occurs have cited 130 beats per minute as the lower limit found in normal subjects[25,26] however no angiographic data were available in these reports It is apparent that the mean values for patients with right coronary artery disease fell near the lower normal limit, but are significantly different from the mean values in patients in the control group The lowest values seen in patients in the control group of 140 BPM is consistent with reports in patients without clinically overt coronary artery disease [26] In a previous study,[5] values for the functional refractory period of the AV node ranged from 365 msec. to 490 msec. The values obtained in this study are consistent with those observations

The clinical implications of this study are evident Patients who have apparent recovery from AV block during acute inferior infarction may have residual conduction defects Conversely patients having right coronary artery disease with a clinical history or electrocardiographic evidence of infarction may have significant differences in some parameters of AV nodal function when compared to patients with less coronary obstruction

Drugs which act on the AV junctional tissues should be used with caution in patients who may have underlying alterations in AV conduction Subclinical conduction defects may be an explanation for the increased sensitivity to digitalis observed in some patients with a tendency to develop atrioventricular block or junctional arrhythmias [27,28]

The results of this study establish that defects in atrioventricular conduction may be found in patients with significant obstruction of the right coronary artery in the absence of acute myocardial infarction These defects may exist in a subacute or occult state in some patients with clinically evident atherosclerotic heart disease

Summary

The purpose of this study was to investigate the occurrence of latent defects in AV conduction in patients with right coronary artery disease Twenty two patients with greater than 50 per cent obstruction of the right coronary artery and a predominant right coronary artery system or pattern were studied with His bundle electrograms and determinations were made of the functional refractory period of the AV node and the point at which AV Wenckebach developed during rapid atrial pacing with a fixed cycle length The patients were studied prior to or at least six months after the onset of clinical or electrocardiographic evidence of acute infarction Similar measurements were made in eighteen control subjects with less than 50 per cent occlusion of the right coronary artery The results showed significant prolongation of the functional refractory period (467 ± 63 msec for patients with right coronary disease versus 408 ± 43 msec in the control group P <0 01)

Phenergan barbiturates or any combination of those) and Group II consisted of 20 patients who received oral premedication (Valium 13 patients) or none (7 patients) Group I was further subdivided into Group Ia where the brachial arteriotomy approach was used for the procedure (32 patients) and Group Ib where the transfemoral percutaneous approach was used (18 patients) None of the patients had any clinical or electrocardiographic evidence suggestive of acute myocardial infarction following the procedure nor did any have a major complication Minor complications such as local arterial problems at the site of entry were not excluded. Patients who had any clinical evidence of liver disease or skeletal muscle disease prior to the catheterization were excluded. Patients with congestive heart failure were included however they were all as compensated as possible during the study

There was no incidence of myocardial infarction complicating coronary arteriography during this study For the sake of comparison with the catheterized patients the enzyme changes 24 hours after the onset of chest pain were reviewed in 20 consecutive patients with straightforward acute myocardial infarction admitted to the Coronary Care Unit This group will be referred to as the comparison group (C Group)

Table I summarizes the grouping of these patients

Results

The SGOT increased modestly above normal following the procedure in one patient in Group I (2 per cent incidence) In the remaining cases the increases were minimal and the values remained within the normal range Table II summarizes the mean values ± the standard error of the mean before catheterization (Pre Cath) and after the cardiac catheterization (Post Cath) The highest post catheterization value noted was 44 units The mean value in C Group 24 hours after myocardial infarction was clearly abnormal and much higher than those observed following catheterization Fig 1 represents a graphic display of the individual values before and after the procedure

The LDH showed insignificant fluctuations with no clearly abnormal rise in any of the patients Table III summarizes our results The values remained within normal limits and there were no significant differences between the values obtained before and after catheterization in any of the groups and no difference between subgroups. The mean value noted 24 *hours after* myocardial infarction was clearly abnormal and much *higher than all values* observed in the catheterized patients Fig 2 displays graphically the individual LDH results

Table I Grouping of study patients

Group I	*Intramuscular premedication pre catheterization*	*50 patients*
Group I *a*	Brachial artery cutdown	32 patients
Group I *b*	Percutaneous femoral approach	18 patients
Group II	No intramuscular premedication	20 patients
C Group	Patients with acute myocardial infarction	20 patients

Table II Mean values of the SGOT

SGOT	*Pre-catheterization*	*Post-catheterization*
Group I	18 ± 1	22 ± 1
Group I*a*	18 ± 2	21 ± 2
Group I*b*	16 ± 1	22 ± 2
Group II	17 ± 2	18 ± 2
C Group	131 ± 21	

Table III Mean values of the LDH

LDH	*Pre-catheterization*	*Post-catheterization*
Group I	58 ± 3	56 ± 2
Group Ia	56 ± 3	53 ± 2
Group I*b*	60 ± 3	59 ± 4
Group II	53 ± 2	52 ± 2
C Group	198 ± 24	

Table IV Mean values of the CPK

CPK	*Pre-catheterization*	*Post-catheterization*
Group I	30 ± 2	111 ± 11
Group I*a*	30 ± 3	102 ± 13
Group I*b*	30 ± 3	129 ± 22
Group II	26 ± 2	32 ± 3
C Group	639 ± 130	

Interpretation of the serum enzyme changes following cardiac catheterization and coronary angiography

Robert A Chahine MD
Leslie M Eber MD
Albert A Kattus MD
Los Angeles Calif

The significance and extent of the changes in serum enzymes following cardiac catheterization and angiography remain an unsettled issue The interpretation of such changes when prolonged chest pain follows coronary arteriography is clouded by the uncertainty of the extent to which the catheterization procedure itself might alter the blood enzyme levels Published studies by several investigators have yielded conflicting results Some authors reported significant increase in serum glutamic oxaloacetic transaminase (SGOT) in up to 50 per cent of cases[1-3], whereas others found no noticeable change[4,5] Lactic dehydrogenase (LDH) was noted to increase above normal in about 5 per cent of cases by some[4] while others saw only insignificant fluctuations within the normal range[5] Creatine phosphokinase (CPK) did not increase following coronary arteriography in one experience[4] while others described impressive rise in about 80 per cent of cases and questioned its value in the diagnosis of complicating myocardial infarction[3,5] The increase in serum enzyme levels noted by some authors was believed to be secondary to local tissue trauma at the arteriotomy site or to some form of myocardial damage[5]

The purpose of this investigation is to document the presence or absence of post catheterization serum enzyme changes in relation to the particular procedure employed The factors considered are the route of catheter introduction, arteriotomy or percutaneous puncture and the administration of intramuscular premedication

Materials and methods

The serum enzymes SGOT LDH, and CPK were determined before and 24 hours after cardiac catheterization and coronary arteriography in 70 consecutive uncomplicated procedures. The determinations were done according to the routine techniques performed at the UCLA Center for the Health Sciences clinical laboratory SGOT (method of Morgenstern and colleagues[6]) LDH (method of Passen and Gennaro[7]), CPK (method of Siegel and Cohen[8]) The normal values in our hospital are as follows SGOT < 40 units LDH < 68 units and CPK < 50 units

The subjects included in this study were either patients with chest pain syndromes mostly secondary to arteriosclerotic coronary artery disease or patients with valvular heart disease where coronary arteriography was also indicated All subjects had right and left cardiac catheterization cardiac output determination by the Fick or the dye dilution technique, a left ventricular angiogram using power injection of 35 to 45 c c of contrast and right and left coronary arteriograms involving an average of 10 manual injections of 6 to 8 c c of contrast Renografin 76 (Meglumine diatrizoate and sodium diatrizoate) was used exclusively in our cases

The patients were divided into two groups Group I included 50 patients who received intramuscular premedications (Valium Demerol

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The patients were divided into two groups Group I included 50 patients who received intramuscular premedications (Valium, Demerol

statements that there are no significant changes in this enzyme level following catheterization[5] The stated incidence of significant rise in 4 8 per cent of patients in one study[4] could be related to the possible presence of liver disease uncompensated congestive heart failure or pulmonary infarction all of which may elevate the LDH There is not enough clinical information in that study to assess this possibility

The CPK changes were impressive in that significant increases were noted in 68 per cent of patients who received intramuscular premedications (Group I) In the group studied without intramuscular premedications (Group II) the CPK rose to 54 in only one patient This value is in the borderline zone but even when considered abnormal the difference between Group I and Group II remains of high statistical significance ($p < 0.001$) The use of intramuscular premedications therefore accounts for the impressive CPK elevations. Whether such injections have been used or not might explain the conflicting reports in the literature describing high incidence of significant CPK increase[3,5] or no significant change[4] However those reports did not specify whether premedications were administered or not. Even in the patients who received intramuscular premedications the mean post catheterization value remained significantly below the one noted 24 hours after acute myocardial infarction (111 ± 11) vs (639 ± 130) $p < 0.005$ however there was considerable overlap of the range of individual figures (23 to 320) vs (72 to 2 440) There was no significant difference in the CPK changes in relation to the type of medication administered intramuscularly in our study or to the approach used whether the procedure was carried out via the brachial arteriotomy or the percutaneous femoral approach The mean post catheterization value for the percutaneous approach was slightly higher than for the brachial approach (129 ± 22) vs. (102 ± 13) but the difference failed to achieve statistical significance The local trauma at a cutdown site or a needle puncture site does not by itself result in significant CPK rise since in Group II no such changes were noted although both approaches have been used.

It is concluded that determination of the serum enzymes before and after catheterization and coronary arteriography constitutes a valuable guideline for the diagnosis of complicating

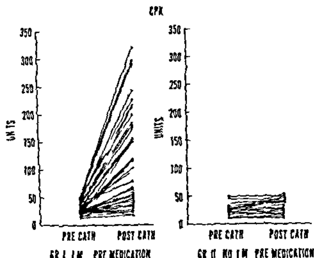


Fig 3 Graphic comparison of the post-catheterization changes of the CPK with and without intramuscular premedication

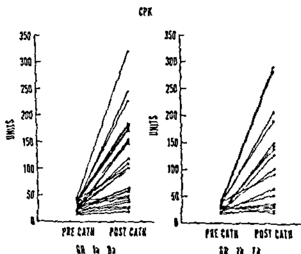


Fig 4 Graphic comparison of the post catheterizations CPK changes in patients studied via the brachial arteriotomy (*Ba*) and the percutaneous femoral approach (FA)

myocardial infarction This holds true for SGOT and LDH whether or not intramuscular premedications are administered, and for the CPK in the absence of such injections In the case where intramuscular premedications are used, the interpretation of the CPK changes becomes difficult because of the overlap of values with those of patients with acute myocardial infarction With this understanding the determination of the serum enzymes should be helpful and informative in patients undergoing coronary angiography particularly in those with left bundle branch block and other electrocardiographic

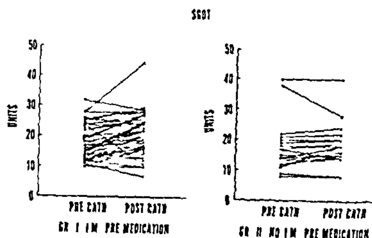


Fig 1 Graphic representation of the SGOT changes following catheterization with and without intramuscular premedication

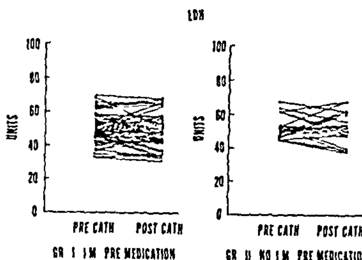


Fig 2 Graphic representation of the LDH changes following catheterization with and without intramuscular premedication

The CPK increased significantly above normal in 68 per cent of patients in Group I (range 23 to 320 units), while only one patient showed a modest increase above normal (from 24 to 54 units) in Group II (incidence of 5 per cent) $p < 0.001$ Table IV summarizes the mean values There was significant increase in the CPK level following catheterization in Group I (from 30 ± 2 to 111 ± 11 $p < 0.005$), while in Group II the increase was minimal and the mean post catheterization level remained within normal limits (from 26 ± 2 to 32 ± 3) The mean post catheterization value for Group I*b* (129 ± 22) was higher than for Group I*a* (102 ± 13) however, the difference was not of a magnitude to achieve statistical significance The mean value in C Group (639 ± 130) was clearly higher than for either group, however there was some overlap between Group I and C Group in the range of individual variations (C Group 72 to 2440 vs Group I 23 to 320 units) Fig 3 graphically compares Group I to Group II and Fig 4 compares Group I*a* to Group I*b*

Discussion

Our data indicate that the changes in serum enzymes following cardiac catheterization and angiography per se are minimal In the absence of myocardial infarction complicating catheterization the most notable post catheterization elevations of the CPK are attributable to the administration of intramuscular premedications Elevations in the level of this enzyme have been previously documented with intramuscular injections alone[9] The introduction of catheters via the arteriotomy or percutaneous routes does not induce a significant elevation of the CPK

This study confirms previous observations that the SGOT does not rise to the abnormal range following cardiac catheterization and coronary angiography[4,5] In the single patient where this enzyme rose above normal the post catheterization value was 44 units which is in the borderline zone and below the usual levels seen in myocardial infarction It is not possible for us to explain the reported incidence of significant elevations of the SGOT in 50 per cent of patients undergoing catheterization or coronary angiography[13] Other factors not specifically looked for in our study might be suspected, such as the types of contrast media used, the number of power injections and the performance of transseptal procedures In one patient not included in this study, where four power injections of contrast were done for evaluation of congenital heart disease the post catheterization SGOT level was 49 units On the other hand in 6 patients where transseptal procedures were performed, one showed abnormal elevation of the SGOT to 58 units The results of this study therefore apply to the patients undergoing routine right and left heart catheterization with left ventricular and coronary angiography using Renografin 76 (Meglumine diatrizoate and sodium diatrizoate) Whether the use of other contrast media or multiple power injections or additional procedures, such as interatrial septal puncture would result in increased incidence of abnormal SGOT elevations remains to be determined.

The LDH data are in agreement with previous

Potential significance of plasma viscosity and hematocrit variations in myocardial ischemia

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While there is still disagreement on various details of the pathogenesis of myocardial ischemia subendocardial necrosis and acute myocardial infarction the destructive nature of each of these processes is ultimately due to the fact that oxygen supply to the involved tissue is insufficient to meet oxygen demand. The severity of the injury is dependent upon the degree to which the supply demand ratio is depressed and the mass of tissue involved Accordingly conditions which compromise oxygen delivery will worsen an existing ischemic state and tend to extend (or precipitate) tissue necrosis

It is generally accepted, on the basis of extensive experimental and clinical observations that the physical characteristics of the blood, primarily hematocrit and plasma viscosity are important determinants of the rate of oxygen transport in the circulation [1-9] The plasma viscosity reflects the level of large asymmetric proteins in the blood and is a sensitive indicator of changes in fibrinogen or globulin concentration being extremely insensitive to the other plasma constituents [10-13] Following myocardial infarction the concentration of fibrinogen increases often by a factor of two to three [14,15] A significant rise in plasma viscosity would therefore be expected, and indeed this has consistently been borne out by experiment[10,11] (also personal communication with Dr J Harkness [5/31/72]) The hematocrit in patients with myocardial infarction has also been shown to be somewhat elevated,[16,17] which would tend, along with the increase in plasma viscosity to raise the *over all level* of the blood viscosity

The reciprocal relation between blood viscosity and blood flow then implies that further reductions in coronary perfusion will occur—in any *area of the heart which* is already maximally vasodilated. Whether or not this effect has any *real clinical significance* or is in fact much too *small to be of importance* is not known This situation is due both to the lack of experimental studies (in which hematocrit or plasma viscosity has been varied following myocardial infarction) as well as the unavailability of quantitative relations between hematocrit plasma viscosity and myocardial oxygen delivery

In this paper we concentrate on the formulation of such quantitative relationships. This is accomplished by developing a mathematical equation which permits examination of the effects of variations in plasma viscosity heart rate and hematocrit as they influence flow of oxygen to the inner layers of an ischemic left ventricle According to the equation significant decreases in oxygen supply can in fact be effected by clinically observed changes in plasma viscosity and to a

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patterns that may make the diagnosis of myocardial infarction more difficult

Summary

The changes in the serum enzymes following cardiac catheterization and coronary angiography remain the subject of controversy and their value in the diagnosis of complicating acute myocardial infarction (AMI) has been questioned In order to evaluate this problem serum glutamic oxaloacetic transminase (SGOT), creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) were determined before (PRE) and 24 hours after (POST) 70 uncomplicated studies Intramuscular premedications were used in 50 (Group I) and 20 had oral premedications or none (Group II) The changes in SGOT and LDH were trivial and the POST values remained within the normal range The CPK increased significantly in 68 per cent of patients in Group I while in Group II it increased insignificantly within the normal range The mean enzyme values from 20 patients admitted to the Coronary Care Unit with straightforward AMI 24 hours after the chest pain were clearly and significantly higher than all the mean POST values however there was considerable overlap of the individual CPK values with those of Group I With this understanding the serum enzymes remain a valuable adjunct to the diagnosis of AMI complicating coronary arteriography

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of oxygen and that 1 ml. of red blood cells contain approximately one third Gm of hemoglobin Any factors which decrease arterial oxygen tension will of course lower the value of the constant 0 0045

Blood viscosity

In order to utilize equation (3) it is necessary to introduce an expression for η the blood viscosity It is quite easy to measure the value of η to a very high degree of accuracy *in vitro* However its proper *in vivo* value has been somewhat elusive This is due both to the non Newtonian nature of blood[4] (implying a viscosity dependence on velocity gradient) and also anomalous phenomena such as the Fahraeus Lindvquist effect[29,30]

When blood is studied *in vitro* it is found that at very low flow rates or velocity gradients the viscosity is many times greater than at high velocity gradients and in fact appears to increase without bound as the velocity gradient is continually lowered. This effect is due to the existence of a *yield stress* (YS) in blood.[4] The YS is the stress required to just initiate flow In ordinary liquids such as water or benzene there is no YS and any stress no matter how small will cause the fluid to flow The YS in blood appears to be due to the formation of a three dimensional network of red blood cells bridged by fibrinogen molecules[4] Furthermore small elevations in hematocrit or fibrinogen lead to quite large increases in YS

At velocity gradients of the order of 100 0 sec.[1] the blood viscosity reaches its lower high shear rate limit.[4] Further increases in velocity gradient no longer reduce the viscosity and blood now behaves like a Newtonian fluid. Rough estimates of the values of the velocity gradient in various parts of the vascular bed in the normal circulation suggest that the velocity gradient is almost invariably much greater than 100 sec [1] and so it might be expected that the high shear blood viscosity is the proper *in vivo* value Indeed all available evidence is consistent with this concept. For example Guyton[6] and Crowell and Smith[7] have noted that in both acutely induced anemia and polycythemia the changes in cardiac output can be explained solely on the basis of changes in high shear viscosity This has also been recently emphasized by Chien[31] and by Sunder Plassman and colleagues[32,33]

According to Sunder Plassman

> "We found an inverse linear correlation with a high regression coefficient between the decrease in apparent whole blood viscosity as measured at high shear and the increase in stroke volume of the heart under these conditions (hemodilution with Dextran 60)"[33]

Gordon[34] observed that increases in *coronary blood flow* during anemia can also be explained almost totally on the basis of decreases in high shear blood viscosity

It may be argued that in myocardial ischemia blood flow is reduced to the point that low shear rate viscosity data more closely corresponds to the true physiological situation. A rough calculation however indicates that even for a 75 per cent reduction in resting coronary flow the average shear rates in the myocardial arterioles (the primary sites of resistance) are still above the value at which non Newtonian effects begin to appear This is consistent with the results of Crowell and Smith and associates[7,9] These authors found that the optimal hematocrit* calculated using a high shear viscosity hematocrit relation was in excellent agreement with that obtained experimentally during hypotensive shock (corresponding to the hematocrit at which the time for the development of irreversible shock was greatest) This suggests that even in a reduced flow situation corresponding to a reduced velocity gradient the high shear viscosity is still the relevant *in vivo* viscosity Clearly however there must exist regions of the myocardium where flow is sufficiently sluggish that low shear rate effects must be considered. The implications of this are considered in a later section

Let us now turn to the selection of a proper high shear viscosity hematocrit relation Available data are well described by both the Vand Equation[4]

$$\eta = \eta_p(1 + 0.025H + 7.35 \times 10^{-4} H^2) \qquad (4)$$

and an expression suggested by Crowell and Smith[7]

$$\eta = \eta_p e^{0.025H} \qquad (5)$$

In both equations η_p is the plasma viscosity If we expand the exponential term in equation (5) we see that

$$\eta = \eta_p(1 + 0.025H + 3.125 \times 10^{-4} H^2 + \ldots)$$

so that both equations agree well at low

*That hematocrit at which oxygen delivery is maximized.

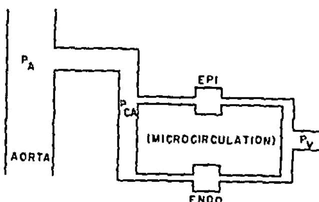


Fig 1 Model of the circulation in the left ventricle P is the pressure in the aorta (A) coronary artery (CA) and vein (V) respectively The microcirculation is divided into epicardial (EPI) and endocardial ($ENDO$) regions

much lesser extent by clinically observed changes in hematocrit. These results are sufficiently striking to suggest that experimental studies are now in order

Subendocardial oxygen transport

Numerous anatomic and physiologic studies have shown that the subendocardium of the left ventricle (SEC) is the site most susceptible to ischemia and necrosis [18,20] consistent with the well known fact that the blood vessels of the SEC are subjected to the greatest extravascular pressures these pressures being maximal during the systolic portion of the cardiac cycle Thus during a certain fraction of each heart beat the SEC is subjected to a "systolic squeeze," which quite literally squeezes the blood vessels to the point where flow is stopped and sometimes reversed in direction Consequently the inner region of the myocardium of the left ventricle is less adaptable to the stresses of atherosclerosis hypertension, and adrenergic stimuli There is also another phenomenon which occurs in the SEC, and may in fact play a far more important role in myocardial ischemia than systolic compression This deals with the shunting of blood away from the SEC during *diastole*, if the difference between mean coronary perfusion pressure and left ventricular end diastolic pressure drops below a value of approximately 40 to 50 mm of Hg [21,23] In addition to the direct experimental confirmation of such an effect, there is also a variety of indirect support [19,24] A good example may be found in the paper by Sugimoto Sagawa, and Guyton [24] These workers showed that for moderate reductions in coronary perfusion pressure the cardiac output curve was unaffected at low left atrial pressures but became significantly depressed at large left atrial pressures The "critical pressure difference" (coronary perfusion pressure–left atrial pressure) was about 50 mm Hg Based on these considerations, we will mainly be concerned with subendocardial flow, and specifically that situation wherein maximum vasodilation has occurred.

In order to examine SEC hemodynamics mathematically, the simplified model for coronary flow which was presented by Winbury and associates[25-6] is utilized (Fig 1) Here a coronary artery epicardially located forms a right angle junction with a "tributary," which feeds both a superficial and a deep region of the myocardium The mean aortic pressure is denoted by P_A the mean pressure at the junction of the tributary by P_{CA}, and the pressure in the collecting veins by P_V The flow rate through the deep region of the myocardium is denoted by Q_{ENDO} in units of ml/100 Gm min

This flow rate may be expressed in the form

$$Q_{ENDO} = F_{DIAS} \frac{P_{CA} - P_V}{R_D} \frac{\text{ml}}{100\,\text{Gm min}} \quad (1)$$

Here F_{DIAS} is the fraction of the cardiac cycle occupied by diastole It is necessary to include this factor since SEC flow ceases during systole R_D (D for "deep") is the resistance to flow This reflects both the viscous resistance of the blood itself and also the caliber of the vessels. In the case of maximum vasodilation we can write[27-8]

$$R_D = \eta \times VR_D(P_{CA} - P_{LVED}) \quad (2)$$

where η is the blood viscosity, VR_D is the vascular resistance and we write $VR_D = VR_D\,(P_{CA} - P_{LVED})$ to emphasize that VR_D is a function of the pressure difference $P_{CA} - P_{LVED}$ P_{LVED} is the left ventricular end diastolic pressure

Combining equations (1) and (2) multiplying by the hematocrit, H and introducing the appropriate conversion factors the rate of oxygen delivery to the subendocardium is found to be

$$FO_2 = \frac{0.0045\,H(P_{CA} - P_V)}{\eta \times VR_D(P_{CA} - P_{LVED})} \times F_{DIAS} \frac{\text{ml } O_2}{100\,\text{Gm min.}} \quad (3)$$

In the derivation of equation (3) it was assumed that 1 Gm of hemoglobin combines with 1 34 ml

Read $VR_D\ (P_{CA} - P_{LVED})$ as VR_D is a function of $P_{CA} - P_{LVED}$

Table 1 Effects of variations in plasma viscosity and hematocrit on oxygen delivery to the subendocardium of the left ventricle*

Hematocrit	*Plasma viscosity (cP)*				
	1 2	*1 4*	*1 6*	*1 8*	*2 0*
30	+17%	No change	−13%	−22%	−30%
37	+19%	+1%	−11%	−21%	−29%
40	+18%	+1%	−11%	−21%	−29%
45	+17%	Reference values	−13%	−22%	−30%
50	+15%	−2%	−14%	−24%	−31%
55	+12%	−4%	−16%	−25%	−33%

Numbe s r f r to per cent changes from control hematocrit of 45 and plasma viscos ty f 1 4

brinogen and in fact increases in fibrinogen concentration above 800 mg per cent have been shown to indicate a poor clinical prognosis with the seriousness of the prognosis correlating quite closely with the magnitude of the maximum fibrinogen increase (levels of 1 300 to 1 400 mg per cent have been reported[14,15]) An increase in fibrinogen concentration from 300 to 800 mg per cent corresponds to approximately a 20 per cent increase in plasma viscosity and consequently according to our model a 20 *per cent reduction in* the total amount of oxygen flowing to the inner layers of the heart per unit time Since η is not quite directly proportional to η_p, a slightly smaller decrease in $\dot{FO}_2$ might be a more realistic figure However elevations in fibrinogen have enormous effects on the low shear viscosity and in those regions of the myocardium where flow is essentially stopped, this would play an important role (as is discussed below) Furthermore elevations in plasma viscosity would tend to impair capillary oxygen exchange[5] It is important to emphasize that only in the case of such severe elevations in fibrinogen levels would we expect to see a marked correlation between fibrinogen and prognosis since clearly for smaller elevations (say to 600 or 700 mg per cent) many other clinical variables would mask the effects of elevated plasma viscosity

Complicating factors

1 Effects of low shear rate As we noted the results in Table 1 are based on the assumption of a high shear rate viscosity being applicable to the subendocardial circulation during ischemia

Let us now consider the consequences of low shear rates existing in various portions of the SEC Clearly in coronary occlusion such low shear regions would be anticipated. For this case equation (6) no longer applies and the more general equation (3) must be used From equation (3) we have

$$\frac{\dot{FO}_2(2)}{\dot{FO}_2(1)} = \frac{H_2 \eta_1}{H_1 \eta_2} \tag{9}$$

for constant P_{CA} P_v P_{LVED} and F_{DIAS} At low shear rates the dependence of η on H and η_p is much more pronounced, and η increases rapidly with both quantities Merrill and colleagues[10] have shown that the yield stress of blood increases by a factor of about 8 when the fibrinogen increases from 300 to 1 000 mg per cent This implies a quite large increase in blood viscosity at low shear rates much greater than the increase at high shear rates for the same change in fibrinogen On the other hand, elevations in hematocrit from 40 to 55 per cent increase the yield stress by a factor of about 3[4,40] These results suggest that elevations in fibrinogen may in fact be more deleterious than suggested earlier In either case however the main conclusion is the same The significant elevations in fibrinogen (or η_p) following myocardial infarction are sufficient to cause marked reductions in $\dot{FO}_2$ The smaller elevations that occur in hematocrit probably play a far less important role

It should be noted that high levels of fibrinogen are also believed to play a role in the development of thromboembolic phenomena primarily

hematocrits At hematocrits in the range 30 to 55 the Vand Equation appears to be slightly preferable to equation (5) Above H = 55, however, Crowell and Smith's[7] equation is definitely superior and in fact the Vand Equation ceases to apply even approximately It is important to note that both equations predict a direct proportionality between blood viscosity and plasma viscosity Available *in vitro* studies suggest that η actually increases somewhat less than in direct proportion to η_p, as a consequence of the effects of plasma viscosity on red blood cell deformation The important point, however is that η does increase significantly with η_p as demonstrated, e g, in a recent *in vivo* study by Meiselman and colleagues[35]

Transport equation

In the following calculations the Vand Equation is used to calculate the high shear viscosity Similar results would be obtained using Crowell and Smith's[7] equation Combining equations (3) and (4) we have for the rate of oxygen delivery to the SEC,

$$FO_2 = \frac{0\,0045H(P_{CA} - P_V)}{\eta_p(1 + 0\,025H + 7\,35 \times 10^{-4}H^2)} \times \frac{F_{DIAS}}{VR_B(P_{CA} - P_{LVED})} \frac{\text{ml } O_2}{100 \text{ Gm min}} \qquad (6)$$

which is the final working equation for the calculation of the effects of hematocrit and plasma viscosity variations

Results and discussion

In the case of constant P_{CA} P_V and P_{LVED} equation (6) implies that

$$FO_2 \sim \frac{H}{\eta_p(1 + 0\,025H + 7\,35 \times 10^{-4}H^2)} \times F_{DIAS} \qquad (7)$$

or in other words the oxygen delivery is proportional to the factor

$$\frac{H}{\eta_p(1 + 0\,025H + 7\,35 \times 10^{-4}H^2)}$$

which reflects the properties of the blood and to F_{DIAS} The direct dependence of FO_2 on F_{DIAS} occurs, of course because of the "systolic squeeze" effect, and illustrates clearly the detrimental aspects of tachycardia in myocardial ischemia (since here F_{DIAS} decreases significantly) as has been demonstrated in two recent experimental studies[19,36] * The effects of variations in H on $\dot{FO}_2$ are not immediately discernible from equation (5), since H appears both in the numerator and denominator Using standard techniques, the value of H at which $\dot{FO}_2$ is maximized is found to be

$$H_{max} = 37$$

which is close to the value of H = 40 reported by Smith and Crowell for which dogs were best able to tolerate the hypoxic conditions of simulated high altitudes[8] and for which the time for the development of irreversible hypotensive shock was greatest.[9] A number of other clinical and theoretical studies support the concept of an optimal hematocrit, with values close to that reported here[37-39]

Let us now be more specific about the effects of variations in H and η_p on FO_T. Consider a situation where F_{DIAS} P_{CA}, P_V, and P_{LEVD} remain unchanged, but the hematocrit and plasma viscosity are varied from (H_1, η_{p1}) to (H_2, η_{p2}) From equation (6)

$$\frac{\dot{FO}_2(2)}{\dot{FO}_2(1)} = \frac{H_2\eta_{p1}(1 + 0\,025H_1 + 7\,35 \times 10^{-4}H_1^2)}{H_1\eta_{p2}(1 + 0\,025H_2 + 7\,35 \times 10^{-4}H_2^2)} \qquad (8)$$

where $\dot{FO}_2(2)$ and $\dot{FO}_2(1)$ are the rates of oxygen flow for (H_2, η_{p2}) and $(H_1$ $\eta_{p1})$, respectively Using as normal values η_p = 1 4 cP and H = 45, the effects of variations in plasma viscosity and hematocrit on $\dot{FO}_2$ have been calculated from equation (8) These results are tabulated in Table I, where we have listed per cent change in $\dot{FO}_2$ vs hematocrit and plasma viscosity

As noted above, elevations in both hematocrit and plasma viscosity following myocardial infarction have been reported The variations in hematocrit seem to be rather slight, and no consistent relationship between hematocrit elevations and clinical course has been demonstrated. This is consistent with Table I, since FO_2 varies very little with hematocrit over the range 30 to 55 Plasma viscosity elevations however, seem to be fairly pronounced. In a personal communication (5/31/72) Dr J Harkness has noted a study of 100 myocardial infarction patients with average elevations of 33 per cent This elevation is primarily due to increases in plasma fi

* Tachycardia also increases metabolic needs, further accentuating the imbalance between supply and demand.

be greatly influenced by alterations in plasma fibrinogen In particular the pronounced elevations in fibrinogen that often follow myocardial infarction may play a role in further development of tissue necrosis

This work also suggests a possible technique in the immediate treatment of myocardial infarction victims, before any elevations in fibrinogen and thus plasma viscosity occurs This of course is an intentional reduction in plasma viscosity to salvage ischemic but not yet necrotic myocardium. The work of Maroko Ginks and colleagues[41,42] suggests that up to at least 3 hours after myocardial infarction resumption of flow is capable of dramatically minimizing infarct size Thus immediate plasmaphoresis or Arvin or urokinase administration (which reduce fibrinogen and η_p) may indeed be a valuable clinical adjunct to the usual CCU procedures * Our results offer a firm theoretical basis for experimental studies of these techniques †

Summary

A simplified theoretical model of the myocardial circulation has been developed. This model indicates that elevated values of fibrinogen and plasma viscosity may play a significant detrimental role following myocardial infarction It is suggested that modification of plasma viscosity through a reduction of fibrinogen concentration may be a useful clinical technique in cardiology Infarct size studies in animals such as those of Maroko Ginks and associates[41,42] in which fibrinogen levels are purposely varied, should be useful in testing these predictions

*A similar suggestion was recently made by Ehrly [43]

†Note that reduction of plasma viscosity has the additional benefit of decreasing myocardial afterload.

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Table II Effects of variations in plasma viscosity on coronary perfusion pressure (P_{CA} [mm of Hg]) for both negligible and severe coronary artery disease

	Plasma viscosity (cP)				
	1 2	1 4	1 6	1 8	2.0
P_{CA} no coronary artery disease	96 9†	96 6	96 3	96 1	95 8
P_{CA} severe coronary artery disease	72 6	70 2	67 7	65 2	62 8

Reductions in P_{CA} are much more pronounced with increases in plasma viscosity in severe disease
†The mean aortic pressure is 100 mm Hg in all cases.

by *modifying the low shear properties of blood.* Thus reduction of fibrinogen concentration post infarction could conceivably have this additional benefit

II Effects of variations in coronary perfusion pressure In the previous calculations, P_{CA} was assumed to remain unchanged following eleva tions in η_p and H Since P_{CA} is determined by the resistance along the epicardial arteries (at con stant aortic pressure), changes in viscosity could conceivably affect this quantity To determine the importance of this effect, it is necessary to ex tend somewhat the mathematical analysis Con sider first the pressure drop through the epicar dial bed (Fig 1) We have in analogy with equa tion (1)

$$Q_{EPI} = \frac{P_{CA} - P_I}{R_S} \quad \frac{\text{ml}}{100\text{ Gm min}} \tag{10}$$

where R_S (S = superficial') is the epicardial resistance and of course F_{DIAS} does not appear since flow continues during systole The pressure drop $P_A - P_{CA}$ is obtained from

$$Q_{EPI} + Q_{ENDO} = \frac{P_A - P_{CA}}{R_{CA}} \quad \frac{\text{ml}}{200\text{ Gm min}} \tag{11}$$

where R_{CA} (CA = coronary artery) is the ex tramural resistance

Solving for P_{CA} between equations (1) (10), and (11), and writing

$$R_{CA} = \eta\, VR_{CA}$$
$$R_S = \eta\, VR_S$$
$$R_D = \eta\, VR_D$$

and
we have,

$$P_{CA} = \frac{\left(\frac{1}{VR_S} + \frac{F_{DIAS}}{VR_D}\right) P_I + \frac{P_A}{VR_{CA}}}{\frac{1}{VR_S} + \frac{F_{DIAS}}{VR_D} + \frac{1}{VR_{CA}}} \tag{12}$$

We see that the viscosity does not directly enter equation (12) It does enter indirectly, how ever in the following manner When the hematocrit increases the blood flow required to the subepicardium decreases. This would tend to cause vasoconstriction and an increase in VR_S On the other hand the increased blood viscosity will automatically reduce blood flow The net effect is therefore a small change *in* VR_S and consequently in P_{CA} Reductions in hematocrit would have the opposite effect, again leading to small changes in VR_S and thus P_{CA} On the other hand increases in η_p at constant hematocrit would tend to cause subepicardial vasodilation and a reduction in VR_S while decreases in η_p would have the opposite effect. The effects of such variations in plasma viscosity on P_{CA} have been calculated for typical values of the different variables and are tabulated in Table II for the cases of severe coronary artery disease (CAD) and no coronary artery disease In the latter case the value of R_{CA} was chosen such that $P_A - P_{CA}$ is small about 2 to 3 mm of Hg For coronary artery disease however $P_A - P_{CA}$ is fairly large as a consequence of a large R_{CA} For this case R_{CA} was taken as 10 times its non diseased value No matter what the particular value of R_{CA} chosen the qualitative results are always the same, namely that in CAD increases in η_p lead to pronounced decreases in P_{CA} This in turn results in a further reduction in SEC blood flow

Discussion

In the previous paragraphs a very general analysis of SEC coronary blood flow during myocardial ischemia was presented According to the results of this analysis SEC oxygenation may

Experimental and laboratory reports

Effect of ventricular premature beats on idioventricular pacemaker activity

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Albany N Y

The response to the dominant pacemaker to ectopic premature beats has been variable as seen in clinical electrocardiography and demonstrated in experimental animal models[1-3] The phenomenon of postextrasystolic slowing of the sinus nodal activity has been commonly seen in clinical electrocardiograms [1] Recently, acceleration of the sinus nodal activity following electrically induced atrial premature beats has been demonstrated in man [2] and in the isolated rabbit heart preparation [3] Fleischmann and Pick[4] have observed in patients with slow idioventricular rhythm that ventricular premature beats are followed by idioventricular beats returning at an interval equal to, shorter than or longer than the dominant cycle length A recent microelectrode study of Klein and colleagues[5] on the isolated canine Purkinje tissue has shown that electrically induced early extrasystoles shorten the returning cycle of Purkinje action potential and the late extrasystoles lengthen the returning cycle The present study was undertaken to investigate the effect of electrically induced ventricular premature beats on the postextrasystolic escape interval of idioventricular beats in an in vivo animal model of complete A V block and idioventricular rhythm

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Methods

Experiments were performed on mongrel dogs anesthetized by an intravenous injection of sodium pentobarbital (30 to 35 mg per kilogram of body weight) Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium A femoral artery was cannulated to record the arterial pressure and to obtain blood samples for the determination of blood gas A femoral vein was also cannulated for the drug administration Arterial blood gas and pH were frequently checked and corrected if needed Lead II electrocardiograms were monitored on a Grass polygraph Complete A V block and idioventricular rhythm was produced by destroying the bundle of His with an electric cautery knife The high interventricular septum was first felt with a finger tip placed through the right atrial wall and the tricuspid valve and the area was then pressed with the finger tip to see whether partial A V block can be induced by the pressure When the A V block occurred, the cautery knife was inserted through the right atrial wall and guided by the finger to the area Electrical coagulation was then applied to the area to destroy the His bundle The destruction of His bundle was evidenced by the appearance of complete A V dissociation and widened QRS complexes on Lead II electrocardiograms

A pair of bipolar stimulating electrodes was attached to the anterior septal margin of the right ventricle in order to deliver pacing and premature stimuli through the electrodes These stimuli were 2 msec in duration and twice the diastolic threshold. When the effect of premature beats was studied during spontaneous idioventricular rhythm premature beats (V_2)

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Methods

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A pair of bipolar stimulating electrodes was attached to the anterior septal margin of the right ventricle in order to deliver pacing and premature stimuli through the electrodes These stimuli were 2 msec in duration and twice the diastolic threshold When the effect of premature beats was studied during spontaneous idioventricular rhythm premature beats (V_2)

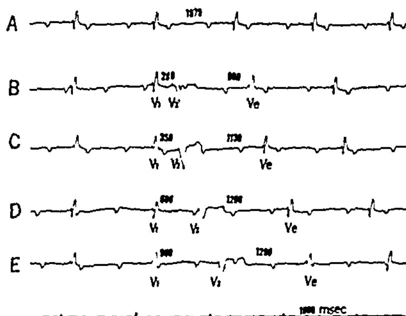


Fig 1 A through E Inverted Lead II electrocardiogram shows idioventricular rhythm after a surgically induced block in the His bundle Ventricular premature beats (V_2) were introduced at various coupling intervals (V_1V_2) in strips *B* through *E* and changes in the postextrasystolic escape interval (V_2V_e) were observed See text for detailed description

were induced at different intervals following every twelfth spontaneous beat (V_1) by means of a Medtronic R wave coupled pulse generator The postextrasystolic escape interval was measured as the interval between the premature V_2 and the first escape beat (V_e) of the same configuration as the basic idioventricular beat, or the V_2V_e interval The effect of premature beats was also studied during ventricular pacing at various cycle lengths The patterns of pacing and premature stimuli were programmed by using a variable interval generator and a series of Tektronix pulse generators The ventricles were driven at a given cycle length and the pacing was interrupted for about 2 5 seconds following every twelfth basic beat (V_1) in order to obtain the interval between V_1 and the first escape beat (V_e) or the basic escape interval (V_1 V_e) Ventricular premature beats (V_2) were then induced at various V_1 V_2 intervals and the postextrasystolic escape intervals (V_2 V_e) were measured In some experiments second premature beats (V_3) were introduced at various V_2 V_3 intervals and the escape intervals following V_3 (or V_3V_e interval) were observed

Results

Premature beats during spontaneous rhythm Fig 1 depicts the typical effect of ventricular premature beats (V_2) on the postextrasystolic escape interval (V_2V_e) during spontaneous idioventricular rhythm The tracings show that complete A V block was present in this dog with slow idioventricular rhythm at a cycle length of 1,070 msec (as indicated in strip *A*) In strip *B*, the earliest possible premature beat with a V_1V_2 interval of 280 msec was followed by the escape interval (V_2V_e) of 980 msec, which was shorter than the basic cycle length of 1,070 msec In *C* and *D*, an increase in the V_1V_2 interval to 350 and 600 msec resulted into longer V_2V_e intervals at 1,130 and 1,200 msec, respectively Further increase in the V_1V_2 interval to 900 msec in *E* failed to produce any further increase in the V_2V_e interval The V_2V_e intervals following the premature beats with longer V_1V_2 were longer than the basic cycle length of 1 070 msec The above results indicate that automaticity of the idioventricular pacemaker was enhanced after early premature beats and was suppressed after late premature beats Similar results were consistently observed in four additional experiments

Premature beats during ventricular pacing Fig 2 illustrates the results of one of the experiments in which the response of idioventricular pacemaker activity to premature beats was studied during ventricular pacing The cycle length of idioventricular rhythm was 1,080 msec before the pacing in strip *A* and the ventricle was paced at a cycle length of 600 msec in *B* through *F* In strip *B* when the pacing

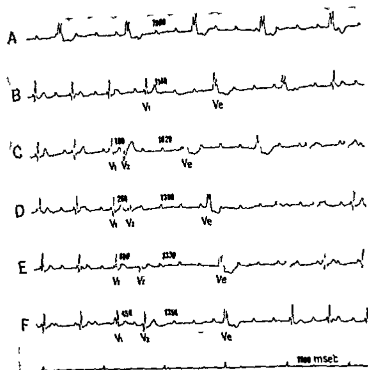
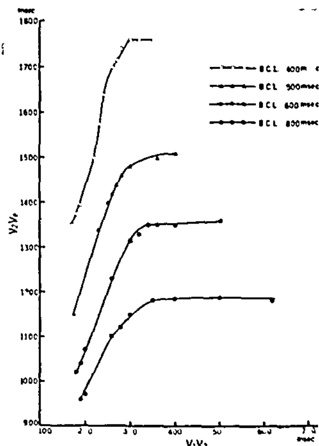


Fig 2 A through F The effect of ventricular premature beats on the postextrasystolic escape interval during ventricular pacing is shown in these Lead II electrocardiograms Strip *A* shows slow idioventricular rhythm before the pacing The basic escape interval (V_1V_e) following the last of 12 paced beats is shown in strip *B*. Ventricular premature beats (V_2) were introduced at various coupling intervals (V_1V_2) in strips *C* through *F* and changes in the postextrasystolic escape interval (V_2V_e) were observed. Detailed description in text

was interrupted for about 2 5 seconds following the last of a series of 12 paced beats the first idioventricular beat escaped at the basic V_1V_e interval of 1 140 msec. Premature beats (V_2) were introduced at various V_1V_2 intervals following the twelfth paced beat in *C* through *F* In strip *C*, the premature V_2 with the shortest possible V_1V_2 of 180 msec was followed by the escape interval (V_2V_e) of 1 020 msec which was shorter than the basic escape interval of 1 140 msec As the V_1V_2 interval was increased to 260 400 and 450 msec in *D E* and *F* respectively the V_2V_e interval was increased above the basic V_1V_e interval of 1 140 msec The results again indicate that automaticity of the idioventricular pacemaker was enhanced after early premature beats and suppressed after late premature beats The same relationship between V_1V_2 and V_2V_e intervals was consistently observed in 15 dogs during ventricular pacing

In five experiments, the effect of premature beats was studied at various rates of ventricular pacing The results of a representative experiment are shown in Fig 3 The V_2V_e intervals are plotted against the V_1V_2 intervals at pacing cycle lengths between 400 and 800 msec (or rates between 150 and 75 per minute) The V_2V_e intervals increased with the decrease in pacing cycle length (or the increase in pacing rate) but the same relationship between V_1V_2 and V_2V_e intervals was seen at all rates of pacing In other words the V_2V_e intervals were shortest at the shortest V_1V_2 intervals and they increased with the increase in V_1V_2 intervals at all rates of pacing

The response of idioventricular pacemaker activity to two successive premature beats was studied during ventricular pacing in a few dogs The results of such an experiment are shown in Fig 4 The effect of single premature beats (V_2) with various V_1V_2 intervals on the V_2V_e interval was first observed The first premature beat (V_2) was then kept constant at the shortest possible V_1V_2 interval, and second premature beats (V_3) were introduced at various V_2V_3 intervals to observe the escape interval following V_3


Fig 3 Effect of ventricular premature beats on the postextrasystolic escape interval during ventricular pacing at various pacing cycle lengths Coupling intervals (V_1V_2) are plotted on the abscissa and postextrasystolic escape intervals (V_2V_e) on the ordinate See text for explanation

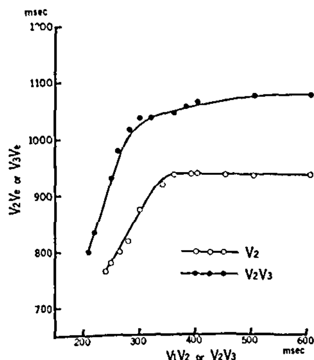


Fig 4 Comparison of effects of single premature beats (V_2) and two successive premature beats (V_2V_3) on the postextrasystolic escape interval Coupling intervals (V_1V_2 or V_2V_3) are plotted on the abscissa and postextrasystolic escape intervals (V_2V_e or V_3V_e) on the ordinate

(or V_3V_e interval) The same relationships between the coupling interval and the postextrasystolic escape interval was seen in the curves for single premature beats (V_2) and two successive premature beats (V_2V_3) However, the escape intervals following two premature beats (V_3V_e intervals) were much longer than those following single premature beats (V_2V_e intervals), indicating greater suppression of the idioventricular pacemaker by multiple premature beats

Overdrive suppression Suppression of the idioventricular pacemaker at the termination of ventricular pacing was seen in many experiments. As seen in Fig 2*A* and *B*, the cycle length of idioventricular rhythm was 1,080 msec before ventricular pacing, and the first idioventricular beat escaped at a V_1V_e interval of 1,140 msec following the interruption of ventricular pacing The overdrive suppression was related to the rate of ventricular pacing as illustrated in Fig 3 The V_2V_e escape intervals increased with the increase in pacing rate (or the decrease in cycle length), indicating greater suppression of the idioventricular pacemaker at faster pacing rates

Fig 5 shows the effect of rapid ventricular pacing on idioventricular rhythm in a dog As shown in strip *A*, the cycle length of idioventricular rhythm was 870 msec. before the pacing The ventricle was rapidly paced at a cycle length of 400 msec (or a rate of 150 per minute) for about 2 minutes and the pacing was suddenly terminated at the early part of strip *B* The first idioventricular beat escaped at an interval of 1,470 msec (much longer than the basic cycle length of 870 msec) Subsequently, idioventricular beats accelerated gradually approaching the basic cycle length as shown in the early part of strip *C*, which was continued from strip *B* The suppression of idioventricular pacemaker was the typical response to rapid ventricular pacing in most experiments, but the overdrive suppression was occasionally followed by abrupt acceleration of idioventricular rhythm probably due to enhanced automaticity at a site other than the dominant pacemaker Enhanced automaticity of this type was observed in strip *C*, and the period of such acceleration lasted from a few beats up to several minutes Strip *D* shows marked suppression of the dominant pacemaker following the termination of accelerated idioventricular pacemaker activity

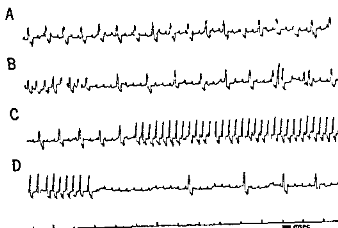


Fig 5 A through D Overdrive suppression and delay acceleration of idioventricular automaticity are shown in these Lead II electrocardiograms See text for detailed description

Effect of drugs The effect of ouabain on the idioventricular pacemaker was studied in five dogs Ouabain was administered intravenously in a dose of 48 μg per kilogram of body weight corresponding to 40 per cent of the estimated lethal dose and the observation was made at about 30 minutes after the injection Fig 6 depicts the results of one of these experiments In comparison with the control the same relationship between V_1V_2 and V_2V intervals was maintained after ouabain but the curve shifted downward, indicating enhanced automaticity of the pacemaker The response to epinephrine infused at a rate of 1 μg per kilogram of body weight per minute was studied in several dogs and the results were similar to those obtained with ouabain

Fig 7 illustrates the results of one of three experiments, in which the effect of lidocaine was studied. Lidocaine was given in a single bolus of 2 mg per kilogram of body weight followed by a continuous infusion of 70 μg per kilogram of body weight per minute A marked upward shift in the curve of lidocaine (marked suppression of the pacemaker activity) was seen without affecting the relationship between V_1V_2 and V_2V intervals. The response to propranolol in a dose of 10 to 20 μg per kilogram of body weight observed in several dogs was similar to that observed with lidocaine

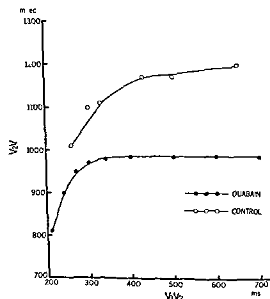


Fig 6 Effect of ouabain on the postextrasystolic escape interval Coupling intervals (V_1V_2) are plotted on the abscissa and the escape intervals (V_2V) on the ordinate

Discussion

The results of this study indicate that there are two general patterns in the response of idioventricular rhythm to ventricular premature beats short escape intervals of the idioventricular beats after early premature beats and the long escape intervals after late premature beats This is in agreement with the study by Klein and associates[5] on an in vitro model of idioventricular rhythm In their microelectrode study on the isolated canine Purkinje tissue the postextrasystolic or returning cycle of Purkinje action potential was shortened after early extrasystoles and prolonged after late extrasystoles Early ex

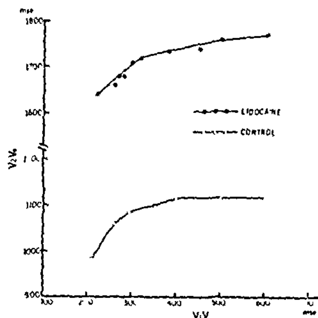


Fig 7 Effect of lidocaine on the postextrasystolic escape interval Coupling intervals (V_1V_2) are plotted on the abscissa and the escape intervals (V_2V_e) on the ordinate

trasystoles which occur during the latter part of repolarization almost always shortened the returning cycle, as a result of the abbreviated duration of the extrasystolic action potentials On the other hand late extrasystoles induced after repolarization is complete led to the Purkinje returning cycle that is equal to or longer than the dominant cycle The suppressed automaticity following late extrasystoles was partly due to an increase in the maximum diastolic potential and a decrease in the slope of diastolic depolarization following the extrasystolic action potential

The present study also demonstrated that the relationship between the coupling interval of ventricular premature beats and the escape interval of idioventricular beats was maintained in the presence of various agencies which are known to alter automaticity of the Purkinje tissue Although the automaticity was enhanced by ouabain and epinephrine and depressed by lidocaine and propranolol the escape interval was shortened after early premature beats and lengthened after late premature beats during the action of these drugs The effect of two successive beats on the escape interval was qualitatively the same as that seen with one premature beat, but the changes observed were the function of the coupling interval between the first and second premature beats and they were more pronounced suggesting a cumulative effect of successive premature beats The same relationship between the coupling interval and the escape interval was observed at all frequencies of ventricular pacing, but suppression of the automaticity was much more pronounced at faster frequencies probably due to the phenomenon of overdrive suppression

The overdrive suppression of intrinsic pacemaker has been reported earlier by many investigators [6,8] In the present study, a consistent suppression of the idioventricular pacemaker was noted when the ventricle was paced at rates between 75 and 150 per minute and the degree of suppression increased with the increase in pacing rate The effect of imposed pacing lasted for several beats after the termination of pacing followed by a return to the basic rate suggesting "warming up' of the pacemaker The overdrive suppression of Purkinje automaticity has been attributed to the slow rate of diastolic depolarization resulting from an increased potassium efflux and excess extracellular potassium [8] In occasional experiments of the present study, a transient acceleration of idioventricular pacemaker activity was noted following the phase of overdrive suppression, suggesting a 'rebound phenomenon Similar rebound phenomena have been noted in an earlier study on the sinoatrial and A V nodal pacemakers [6] There is no definite explanation for the delayed acceleration of idioventricular pacemaker activity following the termination of rapid ventricular pacing

Summary

The effect of ventricular premature beats on idioventricular pacemaker activity was studied in open chest dog hearts with a surgically induced block in the His bundle While the ventricle was paced by basic stimuli at a given rate, the pacing was interrupted for about 2 5 seconds following every twelfth basic beat (V_1) in order to obtain the interval between V_1 and the first escape beat (V_e) or the basic escape interval (V_1V_e) Ventricular premature beats (V_2) were then introduced at various coupling intervals (V_1V_2) and the effect of these premature beats on the postextrasystolic escape interval (V_2V_e) was observed The plot of V_2V_e against V_1V_2 intervals showed that the V_2V_e interval was shortest at shorter V_1V_2 intervals and it increased gradually with the increase in V_1V_2 intervals The V_2V_e intervals at shorter coupling intervals

were much shorter than the basic escape interval (V_1V_2) indicating enhanced automaticity after early premature beats The V_2V at longer coupling intervals were much longer than the basic escape intervals indicating suppressed automaticity after late premature beats The similar response to ventricular premature beats was noted during spontaneous idioventricular rhythm The suppression was more pronounced at faster pacing rates and following two successive premature beats probably due to the phenomenon of overdrive suppression The same phenomena of altered automaticity after premature beats could be observed under the influence of ouabain epinephrine lidocaine and propranolol although these agents either decreased or increased the average escape intervals The results may explain the clinically observed alteration of the idioventricular pacemaker rate following ventricular premature beats

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Experimental atrioventricular block in the course of a hypocalcic electromechanical dissociation

Electrographic and histological data

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Paris France

The needs in calcium of the membrane on one hand and of contractile proteins on the other being different electrical mechanical dissociations may be induced in heart tissue irrigated by hypocalcic solutions

Surprisingly enough this is just as true on the heart as a whole as it is on a simple strip of myocardium

In a previous work on an isolated and perfused rabbit heart [1,2] we showed that all the arrhythmias that can be observed on hearts beating normally could also be observed on hearts arrested in hypocalcic electromechanical dissociation

This report concerns two cases in which we observed certain peculiar electrocardiographic features

Materials and methods

Hearts of male rabbits weighing between 2 and 3 kilograms were very quickly removed after thoracotomy (less than 30 seconds) and were perfused according to Langendorff's technique The isolated heart still beating spontaneously, was immediately immersed in a cup of heparinized warmed saline While the heart was maintained in that fluid a catheter was tied in the aorta (taking care not to force the sigmoid floor) and connected to the perfusion unit.

The infusion pressure was 40 cm of water For that pressure the coronary output is about 20 ml. per minute (This was measured on the fluid flowing into the right atrium after it had perfused the coronary arteries) The contents of the perfused fluid were the following, in mM/L. NaCl 131 NaH_2Po_4 0 98 $MgCl_2$ 0 52 $NaHCO_3$ 11 9, glucose 11, KCl 4 5 $CaCl_2$ 2 (or 0 4) Oxygenation was obtained by a mixture of CO (3 per cent) $+O_2$ (97 per cent) under atmospheric pressure The pH of the solutions was maintained between 7 35 and 7 45 Temperature at the aorta entrance was 37° C

Contraction recording was obtained with an isometric tension captor placed on the apex The electrogram was obtained from bipolar epicardial electrodes (posterior wall of right atrium—left edge of left atrioventricular sulcus)

The atrioventricular conduction pathway was cut with a scalpel after right auriculotomy The septum incision was made below the septal insertion of the tricuspid valve

For histological purposes the septal block was isolated along the following lines upper limit—low interatrial wall two thirds of the way from the upper edge down lower limit—ventricle apex frontally the anteroseptal angle posteriorly the posteroseptal angle The block was fixed in formaldehyde 10 per cent then included whole in paraffin wax The septum was then

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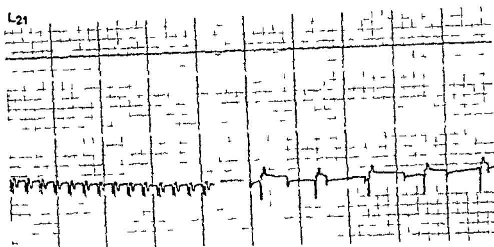


Fig 1 Case No 1 Hypocalcic electromechanical dissociation *Top panel*, no mechanical activity *Bottom panel* (paper speed 20 mm = 1 second) *left* sinus rhythm (150 per minute) *middle* section of the atrioventricular pathway *right* complete atrioventricular block Atrial rate = 52 per minute ventricular rate = 43 per minute

sliced along the frontal plane caudalad and sections were collected every 30 μ Fifty sections were stained and the other kept for further study of certain topographic aspects

Results

Case No 1 After three minutes perfusion of a hypocalcic solution cardiac contractions stopped completely (Fig 1 *top*) Electrical activity persisted the rhythm was sinusal at a rate of 150 per minute (Fig 1 *lower left*)

When the atrioventricular conduction path was cut following the technique described above there appeared a complete atrioventricular block with atrioventricular dissociation the heart being in complete arrest. The escape idioventricular rate was 43 per minute The atrial rate was very slow—52 per minute (Fig 1 *lower right*)

A normocalcic perfusion was then set under way Three minutes later mechanical activity was restored (Fig 2 *top*) To our surprise conduction was also restored between the atria and the ventricles (with possibly a 2 1 A V block) The rhythm was regular at 120 per minute

Case No 2 Experimentation was carried out in several stages.

Perfusion by a hypocalcic solution ($CaCl_2$ 0 4 mmole/L) leads in about four minutes to a total disappearance of mechanical activity (Fig 3 *upper line*) while electrical activity persisted though with gradually decreasing amplitude (Fig 3 *lower line*)

After 20 minutes the atrioventricular conduction path was cut on a heart in complete arrest a complete A V block thus appeared P waves formed regularly at a rate of 171 per minute completely dissociated from the escape idioventricular rhythm whose frequency was 36 per minute (Fig 4)

Perfusion by a normocalcic solution renewed the heart mechanical activity (Fig 5 *upper line*) while conduction disorders gradually faded out at the end of the first minute a second degree A V block was observed, in two minutes a first degree A V block was seen and in three minutes a sinus 171 per minute rhythm (Fig 5 *lower line*) was observed.

A hypocalcic solution was perfused again (Fig 6) Contractions stopped after about three minutes After five minutes a second degree A V block was observed 2/1 A V block was seen at 5 minutes 30 seconds and Wenckebach periods (Mobitz Type I) after seven minutes This last aspect is seen more clearly on magnification (Fig 7)

With another normocalcic perfusion mechanical activity reappeared and a sinus rhythm was gradually restored. First degree A V block appeared after 20 seconds and sinus rhythm after one minute at a rate of 150 per minute increasing to 171 per minute after two minutes and then remaining stable (Fig 8)

Histological data. On the very first section the

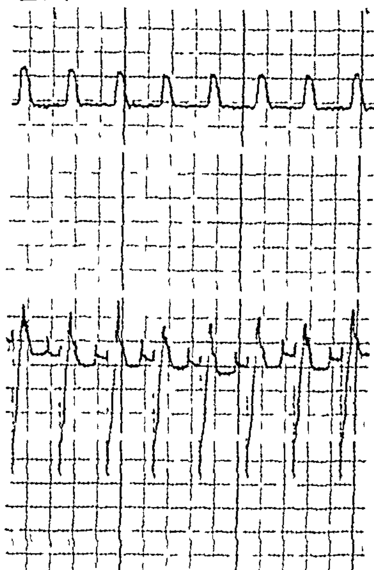


Fig 2 Case No 1 Same preparation as in Fig *1* However the normocalcic solution ($CaCl_2$ 2 mmoles/L) had been perfused for three minutes *Top panel* restoration of heart contraction *Bottom panel* (paper speed 20 mm = 1 second) restoration of atrioventricular conduction

septum appears totally cut across (Fig 9) the upper third being completely severed from the lower part, with no cellular bridge visible The first sections show the upper part of the atrioventricular node This structure is normal all along its length with no fibrous infiltration The bundle of His appears made up of normal cell strips Its bifurcation is clearly apparent as well as the origin of the two divisions (Fig 10) Nowhere is any cellular anomaly to be seen There is no fibrous degenerescence either in the conduction system or in the neighboring myocardium The capillary and arterial branches of the atrioventricular node artery are seen clearly, with no fibrous hyperplasia

Discussion

Electromechanical dissociation We have shown in a previous work on the isolated and perfused rabbit heart that it was possible on a heart in complete arrest to record not only a persistent electrical activity but also all the disorders of excitability or conduction which could be observed on a heart beating normally The lack of calcium impedes the physiological process of excitation-contraction coupling and provokes as a result a failure of the myocardium to contract for lack of use of the energy supplied to the actin myosin bridges in the shape of ATP molecules

However the calcium concentration of the solution should be maintained above a threshold below which irreversible myocardial lesions are sure to occur[34] This threshold calcium concentration probably varies according to species

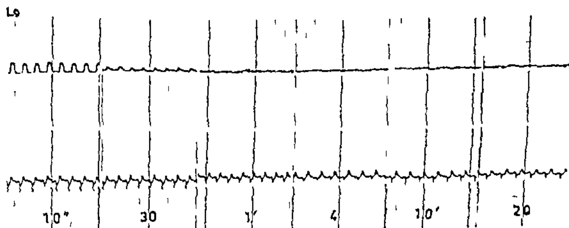


Fig 3 Case No 2 Isolated heart perfused by a hypocalcic solution *Top panel*, gradual weakening of contractions Cardiac arrest towards the fourth minute *Bottom panel* (paper speed 20 mm = 1 second) persistence of electrogram Note the gradually decreasing amplitude of complexes

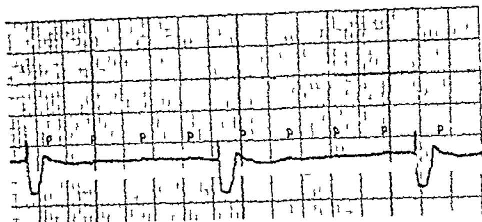


Fig 4 Case No 2 In the heart in complete arrest section of the atrioventricular conduction pathway provokes a complete A V block with dissociation between P waves at 171 per minute and QRS complexes at 36 per minute (paper speed 20 mm = 1 second)

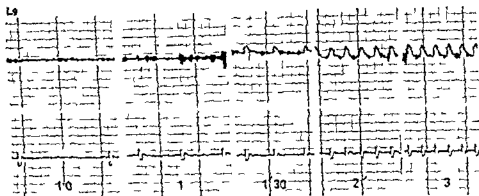


Fig 5 Case No 2 Substitution of a normocalcic solution ($CaCl_2$ 2 mmoles/L) to the hypocalcic one provokes *top panel* gradual return of mechanical activity and *bottom panel* (paper speed 20 mm = 1 second) step by step return to sinus rhythm After 1 minute and 1 minute and 30 seconds second degree A V block. After 2 minutes first degree A V block After 3 minutes 171 per minute sinus rhythm

It is estimated at 0 25 mEq/L in the rabbit (Weiss and colleagues[5]) and at 0 3 mEq/L in the rat (Nieuwendijk and associates[6])

It is on the basis of these data that we chose a $CaCl_2$ concentration of 0 4 mmole/L in our experimentation that is 0 8 MEq/L of Ca^+ which is well above the toxic threshold concentration

Could such data offer the surgeon a type of cardiac arrest that would leave the ECG control unaffected, giving him therefore the possibility of detecting a disorder of A V conduction at any time so that he could either avoid them or on the contrary provoke them? An experimental work on the dog under extracorporeal circulation is at present under way to attempt to answer the question

Paradoxical regression of the atrioventricular block In ten cases out of thirty we cut the atrioventricular conduction pathways on hearts stopped in hypocalcic electromechanical dissociation Four times after what we thought was a complete section we recorded a return to sinus rhythm when the normocalcic solution was substituted for the hypocalcic one

The two cases reported are the best documented as regards electrocardiograms the second being the most detailed on histology The regression of the atrioventricular block is quite surprising considering that as in case No 2 the septum and both branches of the bundle of His were completely severed.

In our opinion two hypotheses could account for the phenomena

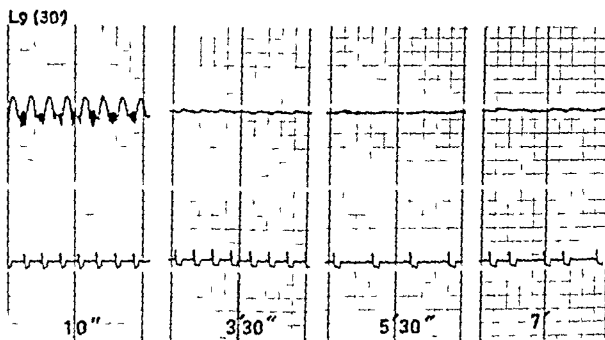


Fig 6 Case No 2 Second change to hypocalcic solution ($CaCl_2$ 0 4 mmole/L) *Top panel*, heart contractions gradually weaken *Bottom panel* (paper speed 20 mm = 1 second) second degree A V block reappears After 5 minutes and 30 seconds 2 1 A V block After seven minutes A V block Mobitz Type I (see magnification in Fig 7)

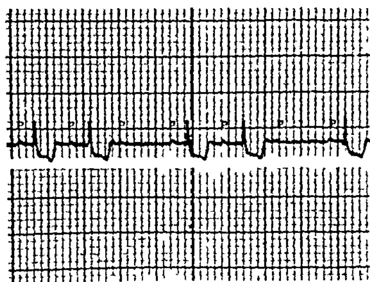


Fig 7 Case No 2 Paper speed 20 mm = 1 second A V block Mobitz Type I (Wenckebach) Magnification of seven minute tracing shown in Fig 6

1 Some strands of the left branch of the bundle of His (which divides rather early) emerge above the section and were spared They are outside the plane of section

2 There are extra Hisian atrioventricular conduction pathways as demonstrated by Sano and co workers[7,8] on the same material

In both cases three problems remain to be solved

1 The ventriculograms are similar both in the escape rhythm in complete atrioventricular block and when the sinus rhythm reappears This implies that the atrioventricular conduction pathway which was spared by the knife (Hisian strand or extra Hisian path) ends up very near the escape site in complete A V block

2 This conduction path does not operate in hypocalcia Deep hypocalcia is known to affect the fast sodium channel and hence the rate of rise of the phase O of the action potential it can thus provoke considerable conduction disorders[9]

3 Finally, the existence of aspects of A V blocks of the Mobitz Type I (or Wenckebach) in a distal A V block is rare but it confirms how difficult is the topographic diagnosis of A V blocks on the basis of electrocardiographic data only and with no recordings of the Hisian potentials[10]

Summary

On a rabbit heart isolated and perfused hypocalcic saline ($CaCl_2$ —0 4 mmole/L) was used to provoke an electromechanical dissociation that is, mechanical activity stopped while electrical activity persisted

On these hearts in complete arrest the atrio ventricular conduction pathway was cut as a result a third degree A V block was recorded. In the two cases reported on substitution of a nor

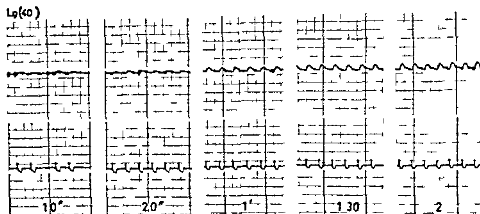


Fig 8 Case No 2 Second change to normocalcic solution ($CaCl_2$ 2 mmoles/L.) *Top panel*, heart contractions gradually strengthen. *Bottom panel* (paper speed 20 mm = 1 second) sinus rhythm gradually reappears Second degree A V block appears after 10 seconds First degree A V block appears after 20 seconds Sinus rhythm appears at the first minute

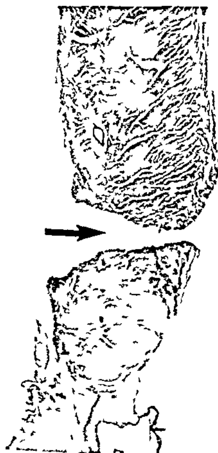


Fig 9 Case No 2 Frontal cut passing through bifurcation of bundle of His. Septum was cut across during the experiment (Hematoxylin and eosin.)



Fig 10 Case No 2 Same section as in Fig 9 on greater magnification. Bifurcation of bundle of His (*H*) (Hematoxylin and eosin.)

mocalcic solution to the hypocalcic one provoked a return to sinus rhythm while the septum had been totally severed as demonstrated by histological examination of case No 2 In this latter case, the passage to A V block or sinus rhythm according to whether the perfused solution was hypocalcic or normocalcic occured gradually, all the types of A V blocks were recorded in particular a second degree A V block (Mobitz Type I) while the experimental lesion was distal The authors discuss these phenomena and in particular the possible role of an extra Hisian conduction pathway Further research might lead to useful applications in heart surgery

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The effect of acute hypoxia on cardiac dysrhythmias induced by mesencephalic stimulation

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Activation of regions of the central nervous system rostral to the medulla oblongata by experimental means may produce severe cardiac rhythm disturbances and electrical stimulation in specific areas of the hypothalamus basal ganglia and the mesencephalon has elicited a variety of supraventricular and ventricular dysrhythmias [1-3] Recent studies from our laboratory have demonstrated a relationship between the type and severity of induced ventricular arrhythmia and the intensity of the electrical stimulus Thus a spectrum of ventricular arrhythmias ranging from ventricular premature contractions to ventricular fibrillation has been produced through graded increments in the intensity of the stimulus to loci within the mid brain [4] These arrhythmias were mediated entirely by an increase in sympathetic efferent discharge

Previous studies have shown that ventilation of animals with low oxygen concentrations activates autonomic centers in the hypothalamus medulla and spinal cord to increase sympathetic efferent impulse traffic.[5,6] More recently Downing and associates[7,8] observed that cerebral hypoxia produced an increase in heart rate in cats which was unaffected by abolition of the arterial chemoreceptors. They suggested, in agreement with the earlier studies that the sensory system primarily responsible for enhanced sympathetic outflow to the heart resided within the high neural structures rostral to the medulla and that it represented an intrinsic functional property of the autonomic centers

Since these studies indicate that both electrical stimulation of regions rostral to the medulla oblongata and arterial hypoxia most likely affect autonomic neurones located within the same or closely similar regions of the central nervous system we have attempted to assess the effect of simultaneous electrical stimulation of the mesencephalon and acute arterial hypoxia on heart rhythm and arterial pressure It might be expected that these physiological variables acting in concert would enhance sympathetic outflow from regions above the medulla to a greater degree than either variable alone and thus produce more significant effects on cardiac function

Methods

Twenty adult cats were anesthetized with alpha chloralose 30 mg per kilogram of body weight intraperitoneally and ventilation was paralyzed with decamethonium bromide Respiration was controlled with a small animal respirator and end tidal CO_2 was continuously monitored with a Beckman CO_2 analyzer The respiration was controlled to maintain constant eucapnea Stainless steel electrodes, 0 5 mm at the tip were guided stereotaxically into regions of the mesencephalon known from earlier studies to evoke strong sympathetic discharge [9] ECG standard Lead II and arterial pressure

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Table I Vagi intact

Cats		Control			Stimulation		
		HR	BP	Rhythm	HR	BP	Rhythm
WITHOUT BETA RECEPTOR BLOCKADE							
1	Room air	200	150/90	Sinus	250	200/110	Sinus
	Hypoxia	230	200/110	Sinus	260	250/120	Ectopic junctional and ventricular tachycardia
2	Room air	180	140/80	Sinus	210	190/100	Sinus
	Hypoxia	220	190/100	Sinus	250	270/170	Sinus pauses junctional and ventricular rhythms
3	Room air	170	130/70	Sinus	200	180/100	Sinus
	Hypoxia	215	170/110	Sinus	250	260/160	Sinus
4	Room air	175	142/90	Sinus	195	170/110	Sinus
	Hypoxia	200	160/100	Sinus	240	210/140	Runs of junctional and/or ventricular tachycardia
5	Room air	160	120/70	Sinus	185	140/90	Sinus
	Hypoxia	190	150/90	Sinus	215	220/150	Multiple ectopic ventricular beats
6	Room air	210	130/80	Sinus	240	170/100	Sinus
	Hypoxia	230	140/90	Sinus	240	200/120	Occasional sinus pauses ectopic ventricular beats
7	Room air	176	145/85	Sinus	190	170/110	Sinus
	Hypoxia	200	180/100	Sinus	210	205/100	Sinus
8	Room air	190	150/90	Sinus	210	181/125	Sinus
	Hypoxia	200	170/110	Sinus	205	200/110	Sinus
9	Room air	170	115/70	Sinus	195	140/90	Sinus
	Hypoxia	190	150/90	Sinus	200	180/110	Sinus
10	Room air	160	120/80	Sinus	180	140/90	Sinus
	Hypoxia	180	140/90	Sinus	200	190/120	Sinus
11	Control	182	135/85	Sinus	195	160/90	Sinus
	Hypoxia	195	160/90	Sinus	205	210/150	Ectopic junctional and ventricular beats
12	Control	175	120/80	Sinus	200	170/110	Sinus
	Hypoxia	190	150/90	Sinus	210	200/115	Sinus
13	Control	165	115/75	Sinus	195	145/90	Sinus
	Hypoxia	180	140/90	Sinus	195	190/120	Ectopic atrial and ventricular beats
WITH BETA RECEPTOR BLOCKADE							
2	Room air	140	120/70	Sinus	136	130/80	Sinus
	Hypoxia	136	120/80	Sinus	134	130/80	Sinus
4	Room air	128	110/68	Sinus	120	115/70	Sinus
	Hypoxia	130	112/70	Sinus	126	114/72	Sinus
5	Room air	116	100/60	Sinus	118	100/60	Sinus
	Hypoxia	120	100/60	Sinus	118	100/60	Sinus
6	Room air	132	110/70	Sinus	130	108/68	Sinus
	Hypoxia	130	108/68	Sinus	130	110/70	Sinus
11	Room air	148	120/80	Sinus	140	130/90	Sinus
	Hypoxia	146	120/80	Sinus	138	128/88	Sinus

Table II Vagotomized

Cats		Control HR	Control BP	Control Rhythm	Stimulation HR	Stimulation BP	Stimulation Rhythm
WITHOUT BETA RECEPTOR BLOCKADE							
14	Control	210	150/100	Sinus	220	160/110	Sinus
	Hypoxia	220	155/100	Sinus	230	175/110	Ectopic ventricular beats
15	Control	215	140/100	Sinus	220	150/110	Sinus
	Hypoxia	220	170/110	Sinus	230	170/115	Sinus
16	Control	195	150/100	Sinus	205	190/120	Sinus
	Hypoxia	210	160/110	Sinus	270	210/130	Ectopic junctional and ventricular beats
17	Control	185	130/80	Sinus	205	160/110	Sinus
	Hypoxia	200	150/100	Sinus	210	190/170	Frequent VPC's
18	Control	190	120/80	Sinus	220	150/110	Sinus
	Hypoxia	210	150/100	Sinus	230	170/120	Sinus
19	Control	180	130/90	Sinus	210	180/120	Sinus
	Hypoxia	200	180/110	Sinus	210	190/120	Frequent VPC's
20	Control	190	110/80	Sinus	215	140/90	Sinus
	Hypoxia	200	130/90	Sinus	270	160/110	Sinus
WITH BETA RECEPTOR BLOCKADE							
14	Control	128	115/70	Sinus	176	130/75	Sinus
	Hypoxia	132	120/75	Sinus	128	126/72	Sinus
16	Control	140	110/70	Sinus	140	120/70	Sinus
	Hypoxia	142	112/72	Sinus	140	120/72	Sinus
19	Control	130	100/70	Sinus	130	110/72	Sinus
	Hypoxia	130	105/72	Sinus	130	110/72	Sinus

were continously monitored on a Sanborn recorder. A Nuclear Chicago constant current stimulator stimulus parameters duration 0.2 sec, 60 Hz, 0.6 to 1.0 Ma for 10 sec was used to elicit an electrical stimulus of sufficient intensity to produce a moderate increase in heart rate and arterial pressure. This site and stimulus intensity were maintained for neural activation throughout the entire experiment. Following these initial interventions arterial blood gases were obtained and a stimulus was delivered during ventilation of the animal with room air. The arterial PO_2 was then lowered to 40 mm Hg (range 37 mm Hg to 43 mm Hg) by breathing 10 per cent oxygen for ten minutes, arterial blood gases were obtained, and the stimulus was repeated. The animal was again ventilated with room air for twenty minutes, propranolol was administered (0.5 mg to 1.2 mg per kilogram of body weight intravenously) and the electrical stimulus was administered on room air and with arterial hypoxia as in the earlier portion of the experiment. In five animals bilateral vagotomy was carried out prior to initiation of all experimental interventions. Following the completion of all experiments, the brain was perfused with 1 per cent potassium ferricyanide in 10 per cent formalin, a frozen section was obtained, and Nissl staining carried out for identification of the electrode site. Electrode placement was verified by histological examination.

Results

Thirteen cats were studied with the vagi intact and seven following bilateral cervical vagotomy (Tables I and II). In all animals ventilated with room air, PO_2 maintained at 92 mm Hg (range 86 to 97 mm Hg) and end tidal PCO_2

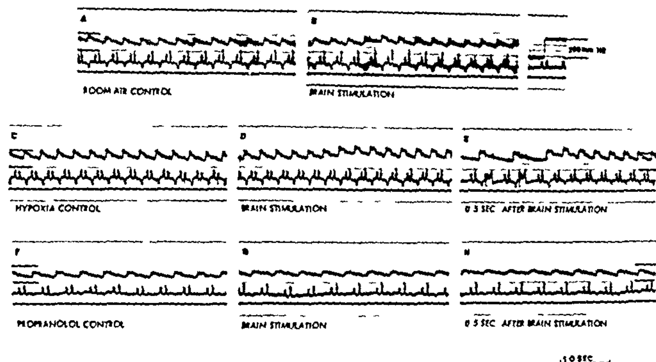


Fig 1 *A* through *H* Effects of mesencephalic stimulation on heart rate and blood pressure in the cat Typical experiment from a cat with vagi intact *A* and *B* stimulation during ventilation with room air increases heart rate minimally and also arterial pressure *C D* and *E* stimulation during arterial hypoxia produces premature complexes probably junctional The arterial pressure and heart rate are increased to a greater degree both during control and with stimulation as compared with room air *F G* and *H* stimulation after administration of propranolol produces no change in heart rate and minimal elevation of arterial pressure

at 37 mm Hg (range 34 to 41 mm Hg) significant increase in heart rate and arterial pressure was evoked with mesencephalic stimulation ($P < 005$) In none of these experiments was an ectopic cardiac rhythm induced with stimulation Institution of arterial hypoxia Po_2 40 mm Hg (range 37 to 42 mm Hg) with maintenance of eucapnea Pco_2 36 mm Hg (range 33 mm Hg to 42 mm Hg), produced a significant increase in heart rate and arterial pressure ($P < 005$) as compared with the control group ventilated on room air Following stimulation of the mesencephalon during hypoxia a further significant increase in heart rate and arterial pressure occurred as compared with the non stimulated hypoxia group ($P < 005$) In 11 of the 20 cats stimulated during acute arterial hypoxia abnormal heart rhythms were evoked which consisted of sinus pauses multifocal ventricular premature contractions, and runs of either ventricular or junctional tachycardia (Fig 1) These arrhythmias were evoked from 5 to 10 seconds following onset of stimulation and were significantly different from the rhythm observed during stimulation while ventilation was maintained with room air ($P < 04$) All observed responses occurred within 10 seconds of the time of onset of the stimulus Following beta blockade with propranolol in 5 cats with the vagi intact and 3 with bilateral vagotomy mesencephalic stimulation on room air failed to produce a significant change in heart rate from control and a minimal but insignificant increase in arterial pressure Acute arterial hypoxia alone evoked no significant change in heart rate or arterial pressure from control with room air, and stimulation of the mesencephalon elicited no change in heart rate and a mild but insignificant increase in arterial pressure No significant differences were observed in the responses in the animal with bilateral vagal section when compared with those animals studied with the vagi intact (Fig 2) The mild pressor responses following beta blockade were most likely due to persisting alpha receptor activation peripherally with sympathetic stimulation

Discussion

The studies reported lend strong support to the concept that an enhancement of autonomic discharge by means of mesencephalic stimulation in combination with acute arterial hypoxia

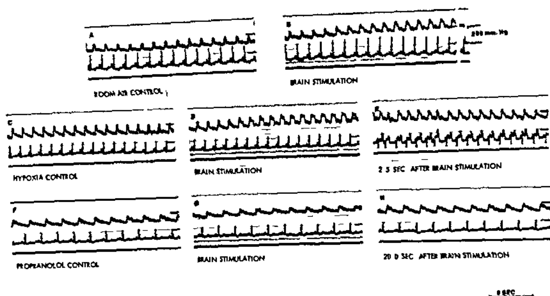


Fig 2 *A* through *H* Effects of mesencephalic stimulation on heart rate and blood pressure in the cat Typical experiment from a cat following bilateral cervical vagotomy *A* and *B* stimulation during ventilation with room air increases heart rate minimally and also arterial pressure *C D* and *E* stimulation during arterial hypoxia produces either junctional or ventricular tachycardia Arterial pressure and heart rate are increased to a greater degree both during control and with stimulation as compared with room air *F G* and *H* stimulation after administration of propranolol evokes no change in heart rate and minimal elevation of arterial pressure

may have a profound influence on the rhythm of the heart as well as arterial pressure Furthermore it appears that these effects are mediated predominantly by the sympathetic division of the autonomic nervous system It should be emphasized however that although acute generalized hypoxia produces increases in sympathetic outflow from high autonomic centers it might also have effects on other sites which could alter heart rate and arterial pressure such as efferent neural fibers neuroeffector function or local myocardial cells. It is not possible from these studies to clarify or answer this question since generalized hypoxia produces simultaneous effects at all sites However the studies by Downing and colleagues[7,8] which clearly show that sympathetic impulse traffic is enhanced in the accelerator nerve with arterial hypoxia in the absence of chemoreceptor activity support the concept that the effect resides in high neural centers Also additional support for a dominant role of central nervous system discharge in evoking such disturbances of heart rhythm is derived from the work of Szekeres and Papp[9] in which isolated hypoxia of the cerebral vascular supply in cats was carried out while the remainder of the trunk was perfused continuously with normally oxygenated blood. These authors show that the threshold to ventricular fibrillation markedly decreased under these conditions though heart tissue was not subjected to the hypoxic stimulus Thus considerable evidence is available to support the concept that hypoxia has predominant effects on neural tissue and presumably on autonomic neurones

These studies have considerable clinical implication in the ill patient with acute respiratory insufficiency It is well known for example that in the respiratory intensive care unit serious cardiac arrhythmias may be observed at a time when respiration is inadequate and arterial blood gases severely altered.[10,11] Furthermore anxiety related to respiratory distress may lead to increased autonomic discharge from higher neural centers at a time when the arterial Po_2 is acutely and frequently severely decreased. The combination of increased autonomic discharge and arterial hypoxia provide the physiological derangement to evoke serious cardiac arrhythmias in such patients This consideration does not rule out other possible effects on heart rhythm which might occur simultaneously such

as increased right sided pressures hypercapnea and acidosis, since these latter factors might add a further stimulus to arrhythmic activity However in this clinical situation, the correction of hypoxia and use of pharmacological agents to alleviate anxiety and decrease sympathetic discharge to the myocardium might be life saving

Summary

1 Stimulation of the mesencephalon in cats during acute arterial hypoxia (PO_2 40 mm Hg) is associated with highly significant changes in heart rate and arterial pressure and frequently with serious rhythm disturbances

2 The changes are significantly greater than those observed when stimulation is carried out while the animals are ventilated with room air

3 The cardiac arrhythmias and pressor effects appear to be mediated by increased sympathetic discharge

4 The possible role of enhanced sympathetic discharge and acute arterial hypoxia in the production of cardiac arrhythmias in the critically ill patient with respiratory insufficiency is discussed

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A 12-lead patient cable for electrocardiographic exercise testing

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In the absence of a generally accepted protocol for treadmill exercise testing we have designed a cable which is simple and inexpensive to construct and is adaptable to any of the more commonly utilized protocols employing partial[1] or full 12 lead[1] electrocardiographic recordings either before during or after exercise Commercially available cables were found to be either inflexible unnecessarily heavy too short unshielded, or limited to only one chest lead. The electrodes designed to be used with these cables were unsuitable for secure attachment to the patient. The patient cable to be reported is adaptable to any single or multiple channel electrocardiographic recorder and permits the pre exercise application of all ten electrodes The purpose of this paper is to report the design fabrication and results of the first 16 months experience with such a cable

Methods

Design considerations In the operation of the standard electrocardiographic recorder the technician switches to seven different lead positions I II III aV_R aV_L, aV_F and V With the switch in the V position a suction cup electrode is moved manually through the six precordial positions Using the cable described in this report, the operator can switch rapidly through six pre attached V leads. That is with the six precordial electrodes in place each electrode lead wire has a separate position in the cable A selector switch has been interposed in the cable and conveniently attached to the recorder so that when the recorder selector switch is in the V position the additional cable switch dials each precordial lead.

The circuit design for the cable is shown in Fig 1 and the component parts in Table I The finished cable which costs approximately 32 dollars for parts is illustrated in Fig 2 and was constructed as follows

Cable construction. Align ten 17 foot lengths of color coded number 28 stranded wire (Table I) Strip one half inch of insulation from one end of each wire Twist and solder the stripped ends together Solder the twisted ends to a pull wire (Table I) with a lap joint so as to minimize its bulk Tie the unstripped ends to a solid structure such as a door knob making sure that each lead wire is taut. A working space of at least 34 feet in length and in a straight line is required. Insert a scriber or awl point in the end of the 24 foot flat braided shield (Table I) to form a hole and bunch the braided shield to maximum diameter and minimum length Slide the braided shield over the pull wire and over the ten lead wires until the end nearest the pull wire covers only one inch of the pull wire near the solder joint. Hold the braided shield at this point with tape and pull the shield so that it covers the ten lead wires tightly over their entire length Untie the unsoldered ends of the ten strands Remove the tape and unsolder the ten lead wires from the

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Table I Materials for cable construction

Item	Quantity	Description	Manufacturer and No.
Rubber tubing	17 feet	Neoprene tubing 3/16 I D 1/32 wall	Wright R 841 18
Wire	170 feet	Number 28 stranded vinyl insulation	Alpha 1852
Switch	One	12 position one pole	Centralab PSA 201
Box	One	2 × 2 × 1¼ with cover	LMB M 018
Connector	One		Switchcraft 12BL6M†
Braided shield	20 feet	Flat braided shielding	Alpha 1230
Connector	One	White tip jack	Johnson 105 701
Connector	One	Red tip jack	Johnson 105 702
Connector	One	Black tip jack	Johnson 105 703
Connector	One	Green tip jack	Johnson 105 704
Connector	Six	Brown tip jack	Johnson 105 708
Grommet	Two	Rubber grommet	General Cement 7566
Knob	One	Bakelite	Kurz Kasch S 647 3L
Lacing cord	10 feet	Flat	Ludlow N6
Pull wire	20 feet	Number 12 solid copper	Belden 8011
Lubricant	As needed	Wire pulling lubricant	Ideal 31 350

17 feet each of the following colors black brown red, orange yellow green blue violet, grey white
†For Hewlett Packard 1511A EKG single channel recorder

pull wire Then solder the end of the shield to the pull wire after wrapping a bit of bare wire around the braided shield end where it covers the pull wire so as to minimize bulk Tie the un soldered end of the braided shield to a door knob an assistant pulls on the free end of the pull wire making the braided shield taut Apply a liberal quantity of wire pulling lubricant to both the pull wire and the braided shield Insert the pull wire into the rubber tubing which will have to be alternately pushed and pulled over the pull wire When the rubber tubing covers the pull wire the assistant again pulls the wire so as to achieve minimum diameter of the braided shield and allow the rubber tubing to be moved gradually onto the braided shield This cannot be ac complished without lubricant or with the wrong size shield or rubber tubing If the tubing is pushed too vigorously it will telescope if it is pulled too hard it will "neck down The best pro cedure is to move the tubing gradually over the braided shield a section at a time with a peristaltic motion alternately pushing and pull ing Cut the cable from the pull wire trim the ends and connect to the switch box which in turn is then connected to the recorder connector according to the schematic diagram (Fig 1)

Using diagonal wire cutters make two op positely directed cuts resulting in a small dia mond shaped hole in the rubber tubing at a point 14 inches from the patient end of the cable Care must be taken to avoid cutting the braided shield which will be exposed through the 1/8 inch hole made in the tubing Use a scriber to spread the shield and expose the wires By mov ing the scriber sideways individual wires can be identified and the desired one selectively ex tracted Extract one inch of the black wire through one hole Repeat the procedure with the white wire Cut each wire at the point where it re enters the patient end of the cable This will result in one inch leads extending from the hole in the cable and will leave the unconnected wires in the last 14 inches of the cable The un connected wires will maintain the diameter of the cable and give support for the jacks which will be laced to the cable Repeat these steps for the other wires in the cable as follows brown and violet wires at 11 inches orange and yellow wires at 8 inches gray and blue wires at 5 in ches and red and green wires at 2 inches Solder the appropriate color tip jack (Fig 1) to each of the leads coming out of the cable and tie them tightly to the cable with lacing cord running be tween the body of the jack and its shell (Fig 2) Screw the shell tightly after the cord is tied The jack can be held more securely if a shallow groove is turned on each shell near the wire end

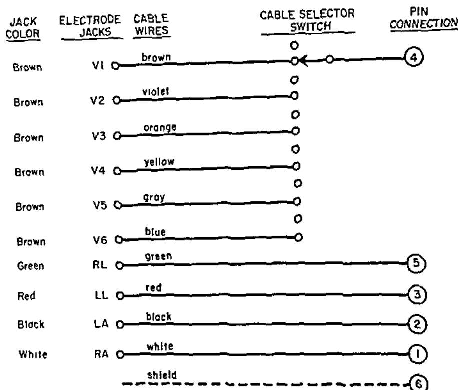


Fig 1 Schematic representation of the cable circuitry Patient end of the cable is on the left recorder end of the cable is on the right.

and another loop of lacing cord tied around the cable and in this groove The tips of some fluid column electrode leads may fit too tightly in these jacks This can be remedied by drilling out the solid metal length of the jack hole with a number 44 drill The depth to be drilled is 3/32 inch as drilling deeper into the contact area will damage the jack Each jack is then labelled.

Patient application. Meticulous technique in skin preparation and application of electrodes is recommended in order to obtain optimal recordings

The skin is prepared according to the general method of Sheffield.[2] The patient s skin electrode sites are cleaned with acetone and then marked with a broad tipped permanent ink felt pen Each site is dermabraded using a Busch and Company No 6 round dental finishing burr* with a straight hand piece The burr is held in a model 270 series 66 2 Dremel Moto tool† The spinning burr is applied with just enough pressure to clear a spot of ink a few millimeters in diameter In this way only the keratin layer is removed, reducing skin resistance ten to fifteenfold.[3]

Ten Hewlett Packard patient electrodes No 14057C* with double stick electrode adhesive discs (part no 14029A) are filled with electrode paste The electrode wells are filled with paste using a disposable syringe without needle Complete and clean filling can be assured by slightly overfilling the well and then turning the electrode upside down on a flat hard, absorbent surface and rubbing in a forward direction once or twice The limb and chest leads were applied in the anatomical positions recommended by Mason and colleagues[4,5] arm leads in the infraclavicular fossae leg leads on the lower abdominal quadrants above the iliac crests and the six precordial leads in the standard positions. We have applied the leg electrodes with the patient supine but the others with the patient sitting Electrode position can change dramatically between these two postures and movement of thick skin folds or breasts can cause significant electrode displacement.

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*Hewlett Packard, Waltham, Mass.

Table I Materials for cable construction

Item	Quantity	Description	Manufacturer and No.
Rubber tubing	17 feet	Neoprene tubing 3/16 I D 1/32 wall	Wright R 841 18
Wire	170 feet	Number 28 stranded vinyl insulation	Alpha 1852
Switch	One	12 position one pole	Centralab PSA 201
Box	One	2 × 2 × 1¼ with cover	LMB M 018
Connector	One		Switchcraft 12BI 6M†
Braided shield	20 feet	Flat braided shielding	Alpha 1230
Connector	One	White tip jack	Johnson 105 701
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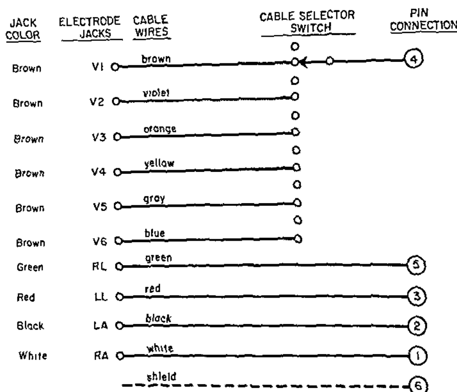


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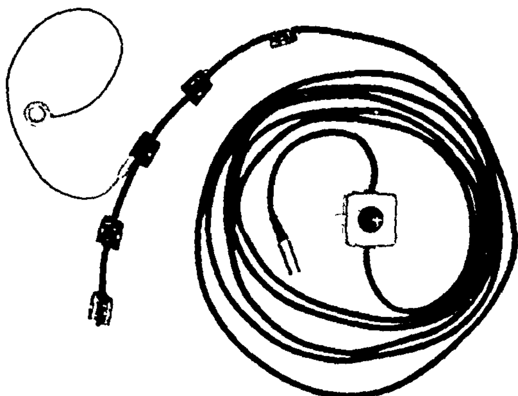


Fig 2 Photograph of the cable electrode system

The electrode leads are fitted into their respec tive jacks on the cable which is attached to the recorder The center of the cable can be looped over an overhead ceiling hook to avoid tension on the electrodes Partial or full 12 lead electrocardiograms with the patient at rest or exercising in the supine sitting or standing postures can then be obtained. When recording from the precordial leads the recorder selector switch must be moved to a neutral position before moving the intra cable selector switch to successive precordial leads In this way the stylus never moves from the baseline position between leads

Results

This cable was tested in more than 230 graded treadmill exercise tests in the Cardiac Research Laboratory at the University of Cincinnati dur ing a 16 month period The flexible shielded ca ble has permitted a baseline which has been flat and artifact has been eliminated except for con ditions of extreme body, arm or hand motion or severe muscle tremor The tracings obtained even during running on the treadmill have been interpreted easily by simple inspection (Fig 3A) Each patient also had supine and standing con trol electrocardiograms with and without hyper ventilation No baseline wander occurred even with deep excursions of the chest. Use of the low noise electrode cable system permitted easy evaluation of ST segments during exercise in all patient studies

Prior application of all ten electrodes to the patient improved the diagnostic sensitivity of the treadmill test. An example of an abnormal ST segment depression which disappeared im mediately after exercise is illustrated in Fig 3B this example would have been missed with out continuous monitoring Two exercise tests were stopped because of ST elevation in the in ferior leads (Fig 3C) Not infrequently exercise was stopped because of ventricular arrhythmias (Fig 3D)

The cable has been sturdy and reliable No repair has been necessary

Discussion

The value of submaximal and maximal exer cise testing in predicting the presence of signifi cant coronary artery disease in asymptomatic subjects and in patients with atypical chest pain has been emphasized[6,7] Both the sensitivity of the test which is a function of developed heart rate and the safety of the procedure require on line monitoring and recording of technically

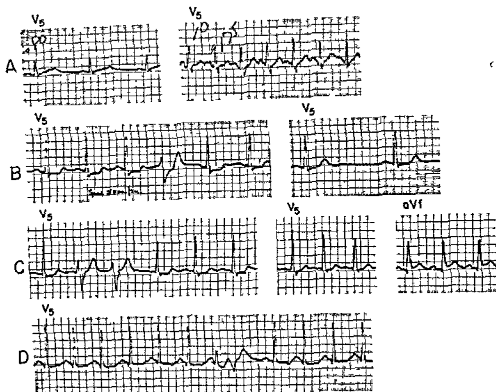


Fig 3 *A* through *D* *A*, The *left hand* panel is a control electrocardiogram (Lead V_5) The *right hand* panel illustrates a recording taken while the normal subject was running on the treadmill at 4 2 m p h and 16 per cent grade (Bruce Stage 4) *B* These recordings were obtained from a patient with angiographically documented significant coronary artery disease The *left hand* panel demonstrates an in exercise positive test (Lead V_6) A single ventricular premature contraction was recorded. There was rapid reversion to normal immediately postexercise (*right hand panel*) *C*, Significant coronary artery disease was documented by coronary angiography in this patient. The *left* panel shows a positive response at four minutes of exercise (Lead V_5) Two ectopic beats were recorded. The *middle* panel (Lead V_5) demonstrates reversion of the pattern to normal shortly thereafter an apparent example of the walk through phenomenon An inferior lead recording (Lead aV_F) taken at the same time as the *middle panel* (Lead V_5) showed significant ST elevation, however (*right panel*) The test was terminated although the patient did not develop angina pectoris *D* An example of coupled multifocal premature ventricular contractions which immediately terminated the exercise in this 24 year old woman with the late systolic click syndrome All recordings at a paper speed of 50 mm per second.

good electrocardiograms in several leads A single protocol for electrocardiographic stress testing which is applicable to all circumstances has not been described. For the test to be useful to the busy practitioner with one technician and limited office space the requirements are different from those of the exercise physiologist with a well equipped and staffed laboratory This cable is applicable to both situations

The cable has several advantages not available with commercial products Application of all ten electrodes to the patient prior to exercise enhances the diagnostic sensitivity of the test Any or all of the 12 leads can be recorded before during and after exercise as well as monitored by oscilloscope It has been our practice to begin a recording just prior to stopping the treadmill so as to obtain a continuous tracing while the patient assumes a sitting or lying position Prior application of electrodes and cable frees the physician to observe the patient while the technician obtains the tracings If the Master two step test is employed, the usual postexercise delay due to reattaching electrodes and the electrocardiograph cable connection is obviated. The true heart rate response can be determined and some false negative tests can be eliminated. Abnormal ST segment shifts may disappear soon after exercise is stopped and may be missed because of even a brief delay in recording (Fig 3B) There

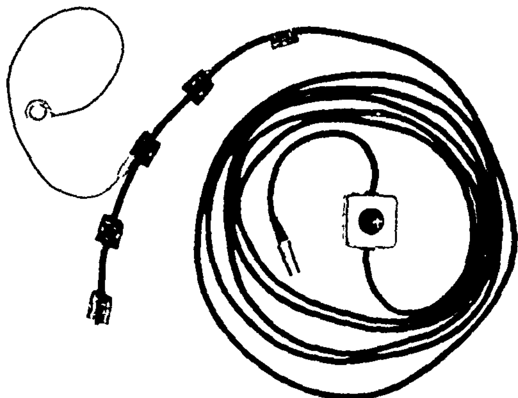


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Prior application of all ten electrodes to the patient improved the diagnostic sensitivity of the treadmill test. An example of an abnormal ST segment depression which disappeared immediately after exercise is illustrated in Fig 3*B* this example would have been missed without continuous monitoring Two exercise tests were stopped because of ST elevation in the inferior leads (Fig 3*C*) Not infrequently exercise was stopped because of ventricular arrhythmias (Fig 3*D*)

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The value of submaximal and maximal exercise testing in predicting the presence of significant coronary artery disease in asymptomatic subjects and in patients with atypical chest pain has been emphasized[6,7] Both the sensitivity of the test which is a function of developed heart rate and the safety of the procedure require on line monitoring and recording of technically

The effect of acute pulmonary artery obstruction on the dog electrocardiogram

Knut Rasmussen M D *
Kåre Michelsen M D
Oslo Norway

Electrocardiography (ECG) has an established although modest, role in the diagnosis of acute pulmonary embolism There is however no general agreement regarding the frequency with which ECG changes occur in pulmonary embolism what type of changes are typical or about their pathogenesis Few experimental studies have been designed to answer these questions The aim of the present study was to clarify (1) what kind of changes in the ECG complexes follow from a *controlled* acute obstruction of the main pulmonary artery in the dog? (2) at which level of obstruction are changes induced? and (3) how do these changes compare with the theoretically expected ECG changes in right ventricular dilatation?

Material and methods

Ten mongrel dogs were given intravenous phenobarbitone (up to 30 mg per kilogram of body weight) to the point of light anesthesia with adequate self maintained respiration A Dotter Lukas double lumen catheter (USCI 5262) was introduced through the right jugular vein to the main pulmonary artery This procedure was not accompanied by changes in right ventricular pressure or in the ECG

The ECG was recorded with the axial lead orthogonal system as developed for dogs[1] using needle electrodes kept in a stable position The dogs were placed on the left side with the legs in the mid position[2] and were not moved during the procedure Scalar X, Y and Z leads were recorded with an Elema Schonander Mingograf 34 using both 50 and 250 mm per second paper speed. Vector loops were photographed in the horizontal right sagittal and frontal projections using a Sanborn amplifier and oscilloscope Maxima and minima were measured from the scalar leads while angles and instantaneous vectors were manually derived from the loops Ordinary orientation of axes and angles were used[3] The ECG was always perfectly stable before the onset of each experiment

Pressures were measured through the catheter lumen ending 1 cm proximal to the balloon Femoral artery pressure was measured through a short catheter inserted into the artery in four dogs Angiography was not performed

Each experiment consisted of rapid inflation of the balloon with various amounts of radiopaque contrast (1 to 15 ml) under continuous fluoroscopic control The volume of the balloon was thereafter kept constant for about 10 minutes Thereafter the balloon was rapidly deflated. Right ventricular or pulmonary artery pressure femoral artery pressure and the ECG were continuously recorded during the procedure A complete set of scalar and planar ECG data was recorded before and after each experiment and during stable pulmonary artery obstruction from two minutes after the inflation In each animal from 5 to 10 inflation experiments were performed, usually with a gradual increase in obstruction from experiment to experiment, and with a minimum recovery time of

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are advantages in multiple lead monitoring We stopped two exercise tests because of ST elevation in the inferior leads (Fig 3C), and several were discontinued because of ventricular arrhythmias (Fig 3D) The tracings are of good quality during strenuous exercise and even during running (Fig 3A) Precise in exercise heart rate becomes easy to determine from the low noise tracing A cardiotachometer would not be triggered by false signals A low noise electrode system without additional cable artifact simplifies identification of diagnostic ST segment changes The cable can be applied to any type of conventional exercise test and protocol, using either a standard 12 lead system or any modification of this lead system The cable can be adapted to any electrocardiographic recorder so that available existing electrocardiographic recording equipment can be utilized.

In view of general interest in extending the use of submaximal exercise testing to areas such as rehabilitation of patients following myocardial infarction functional capacity determination, therapy evaluation, and arrhythmia diagnosis this multipurpose cable could have increasing application

Summary

A simple electrocardiographic cable for use with exercise testing has been developed which has proved to have many advantages over commercially available cables used with standard single channel recorders It can be adapted easily for multiple channel equipment.

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pressure was raised to above 40 mm Hg changes were induced in all dogs The pattern of changes varied to some degree from animal to animal but there was a complete reproducibility in each animal

For quantitative analysis one experiment from each of the two hemodynamic states was selected from each dog Only ECG changes not accompanied by QRS widening was included in this analysis. The results are summarized in Ta ble I Since observations from one dog were lack ing in both hemodynamic states two slightly different groups each consisting of 9 animals were formed.

In the compensated state definite but modest ECG changes were found in all dogs The most consistent observation was a counterclockwise rotation of all parts of the QRS loop in the horizontal plane The only consistent changes in voltage measurements was a reduced amplitude in both directions in the Z lead and the slight superior shift of the maximal T vector The other QRS amplitude measurements showed inconsis tent changes Since the magnitude of the instan taneous QRS vectors was essentially unchanged and the rotation in the horizontal plane was ob served in all dogs it was obvious that the differ ing responses of QRS amplitude data reflected the initial direction of the maximal vectors A rotation in the same direction resulted in some animals in an increased and in others in a decreased amplitude in a certain lead, depend ing on whether the maximal vectors became more or less parallel with the lead axis

During the shock state the changes were more marked but had in general the same direction as in the compensated state Consistent and marked changes were found both for ampli tude and for angular measurements. The QRS changes were again most marked in the Z lead, particularly in the anterior component (Z min) which in average was reduced by about 40 per cent. The observed changes in QRS angles in the horizontal and sagittal plane may be considered mainly as an expression of this reduced Z lead amplitude In addition a small but significant left axis shift was found in the frontal plane The significant changes in the maximal T vector were found in Leads Y and X. The development of a large ST vector directed superiorly and to the right was specific and characteristic for the shock state.

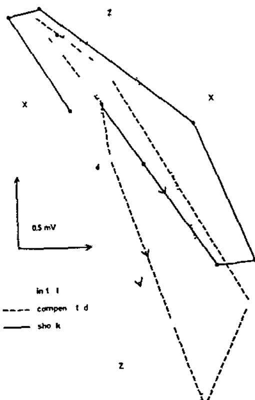


Fig 1 Averaged horizontal plane QRS vector loops from before balloon inflation during compensated pulmonary ar tery obstruction and during obstruction leading to shock Each point represents a 5 msec vector up to the 30 msec vector The last point of the loop indicates the ST vector which is absent in the two first situations but substantial during the shock state The changes between the two first loops is somewhat smaller than those really observed, since the animal that did not enter the compensated state was not quite representative The direction of changes is however correct

It should be remembered that with so few ex periments in each group almost complete con sistency of changes is required in order to reach a statistically significant result Thus the in crease of X lead amplitudes in both directions and of the superior component of Lead Y (Y min) did almost reach statistical significance and may be essential parts of the ECG pattern of acute pulmonary artery obstruction

The P waves were unchanged during both levels of obstruction in most animals and no general pattern of P wave changes could be defined.

In order to find out whether the total amount of QRS forces changed, the sums of the instan taneous 5 msec spatial vectors (Σ QRS) were

Table I Comparison of some ECG measurements before and during pulmonary artery obstruction

Parameter	Compensated state (N=9)				Shock state (N=9)			
	Initial mean	Obstruction mean	Change mean	P	Initial mean	Obstruction mean	Change mean	P
OPTIMA (mV)								
X max	1 40	1 51	+0 11	N.S	1 37	1.55	+0 18	NS
X min	0 76	0 81	+0 05	N.S	0 74	0 85	+0 11	NS
Y max	2 51	2 42	−0 09	N.S	2 65	2 51	−0 14	NS
Y min	0 91	0 96	+0 05	N.S	0 81	0 91	+0 10	NS
Z max	1 33	1 16	−0 18	<0 05	1 31	1 16	−0 15	NS
Z min	2 78	2 56	−0 22	<0 05	2 76	1 62	−1 14	<0 001
ST X	+0 01	+0 01	0 00	N.S	+0 01	−0 22	−0 23	<0 02
ST Y	−0 01	−0 01	0 00	N.S	−0 01	−0 22	−0 22	<0 0?
ST Z	−0 03	−0 02	+0 01	N.S	−0 03	−0 07	−0 04	NS
T X	+0 07	+0 01	−0 06	N.S	+0 12	−0 28	−0 40	<0 05
T Y	+0 36	+0 23	−0 14	≃0 01	+0 39	−0 06	−0 45	<0 001
T Z	−0 56	−0 51	+0 05	N.S	−0 59	−0 68	−0 09	NS
Σ QRS	11 9	11 4	−0 5	N.S	11 6	10 1	−1 5	<0 02
ANGLES (degrees)								
5 $msec_H$	94	76	−18	<0 005	93	56	−36	<0 001
Z min_H	75	70	−6	<0 005	76	51	−25	<0 001
Z max_H	251	240	−11	<0 005	251	232	−19	<0 05
Z max_{SR}	209	219	+10	<0 005	198	215	+17	<0 001
Y max_F	68	68	0	N S	67	57	−10	<0 0?
T_H	87	95	+8	N.S	80	104	+24	<0 02
T_{SR}	36	17	−19	<0 05	31	−2	−33	~0 025

Abbreviations X max, etc = maximal positive deflection in Lead X, etc X min etc = maximal negative deflection in Lead X, etc TX, etc = spatial coordinates of maximal spatial T vector 5 msec H, etc = 5 msec vector in horizontal plane etc N.S = not significant ΣQRS = sum of spatial 10 msec vectors

at least 15 minutes and a complete recovery of heart rate, pressures and ECG between each

The t test for paired differences (two tailed) was used for the statistical evaluation of the results The ECG recorded during obstruction was always compared with the immediately preceeding base line recording

Results

Hemodynamic response Two types of hemodynamic responses occurred The first type was seen during moderate pulmonary artery obstruction In these instances the right ventricular systolic pressure increased rapidly to a level which remained stable until balloon deflation The femoral artery pressure remained unchanged and right ventricular diastolic pressure was only moderately increased Contrast injections proximal to the balloon revealed rapid pulmonary artery blood flow The clinical condition of the dog was good

At a certain level of obstruction, however a second kind of response was observed The initial increase of systolic pressure proximal to the balloon was followed by a gradual fall indicating failure of the right ventricle At the same time femoral arterial pressure fell progressively and the right ventricular diastolic pressure increased markedly Mechanical alternans were seen in several animals at this stage and contrast injection in the pulmonary artery showed slow circulation Advanced tachypnea developed Various arrhythmias were seen but were not subjected to further analysis

These two hemodynamic responses are referred to below as the compensated and the noncompensated or shock state Despite the lack of systemic arterial pressure recordings in several animals all experiments could easily be classified as belonging to one or another of the two patterns The maximal right ventricular systolic pressure which could be maintained without shock varied from 50 to more than 100 mm Hg

Changes in ECG complexes Small obstructions leading to a 10 to 20 mm Hg increase in the right ventricular systolic pressure were not associated with any changes in ECG, but when the

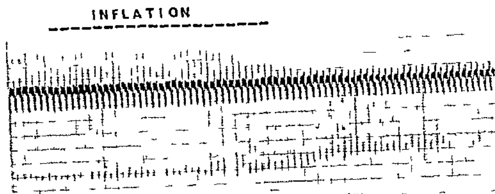


Fig 3 Continuous record of Lead Z during balloon inflation *(stippled line)* following constant obstruction leading to shock Paper speed 5mm /sec (1 second between each solid vertical line) 10 mm = 1 mv Positive deflection = posteriorly negative = anteriorly Both positive and negative Z lead deflections are greatly diminished and the changes occur during the last part of balloon inflation simultaneously with the right ventricular systolic pressure increment When the obstruction is stable (from the end of the stippled line on) the ECG is also stable

deflation of the balloon, they reverted within 3 to 5 beats This stability and reversibility were found also for the shock state in which the hemodynamic conditions deteriorated continously during the obstruction

In three animals another type of ECG change was observed not included in the presentation till now These changes appeared during severe obstruction after a period in which the common types of ECG changes had been present they were accompanied by widening of the QRS complex and they reverted more slowly during several minutes These changes were interpreted as right bundle branch block induced by the stretch of the right ventricular wall and were not subjected to further analysis

Relationship between ECG changes and degree of obstruction As described a progression of the ECG changes was seen from the compensated to the uncompensated state when the group was considered as a whole When all the recordings at different steps of obstruction in the individual animal were considered, this pattern became even clearer From the level where the first ECG changes appeared they always increased progressively with an increasing degree of obstruction and correspondingly subsided with a decreasing obstruction with the same rapid time course as described above Thus in the compensated state there was a relationship between the right ventricular systolic pressure and the ECG changes (Fig 4) When incompensation occurred, this relationship was broken since the pressure then fell with increasing obstruction

Discussion

The results of this study may be summarized as follows

1 An abrupt obstruction of the main pulmonary artery induced definite changes in both QRS and T waves and loops in all dogs

2 In spite of individual differences a characteristic pattern of ECG changes could be defined. In the hemodynamically compensated state this consisted mainly of a counterclockwise rotation of the total QRS complex in the horizontal plane and a superior shift of the T wave

3 In the shock state the changes were still more marked Both anteriorly and posteriorly oriented QRS forces were greatly diminished. The T was dislocated further superiorly and to the right and a large ST vector appeared. This vector was found to be a specific and sensitive indicator of the shock state

4 The changes appeared and disappeared within a few seconds

5 A relationship between the degree of obstruction and the degree of ECG changes was observed.

The hemodynamic observations pointed towards a clearly defined two step response to progressive pulmonary artery obstruction This is in good accordance with recent more elaborate studies in dogs[4-9] with direct observations in dogs[10,11] and with clinical observations in

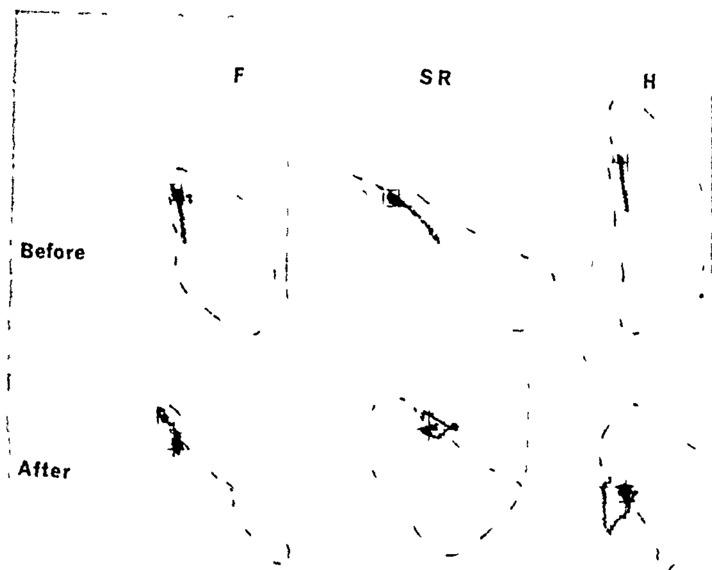


Fig 2 One representative example of vector loops in the frontal *(F)* sagittal right *(SR)* and horizontal *(H)* plane before obstruction *(Before)* and 3 minutes later during stable balloon obstruction leading to shock *(After)* The right ventricular systolic pressure rose from 20 to 50 mm Hg and fell subsequently The anteriorly oriented QRS forces are greatly diminished the septal vectors are dislocated to the left and the terminal part of the QRS is slightly dislocated posteriorly and to the right A large ST vector oriented back right superior is created and the T loop is dislocated superiorly

calculated There was a small but non significant decrease in this sum in the compensated state, but during shock a significant reduction occured (Table I)

For visualization of the described changes average horizontal plane QRS loops were constructed from the mean values of the 5 msec instantaneous vectors up to 30 msec (Fig 1) *These loops are smaller than the true average* loops since straight lines have been drawn between the points The changes may be summarized as a progressive counterclockwise rotation of the total QRS loop This includes leftward dislocation of the initial vectors, posterior dislocation of the maximal anterior vectors, and a dislocation of the terminal part of the QRS loop backwards and to the right The horizontal projection of the ST vector is seen in the figure, and the vertical component of this vector is given in Table I Averaged frontal and sagittal loops were not constructed, since the only *consistent* changes in the Y lead was found to be a downward shift of the 5 msec vector in all cases and an upward shift of the terminal QRS vectors in most cases

One typical example of ECG changes in the shock state is shown in Fig 2

Time course of ECG changes The changes described above had a uniform and consistent time course They arose within the first 3 to 5 beats after balloon inflation and were completely stable during constant obstruction (Fig 3) A

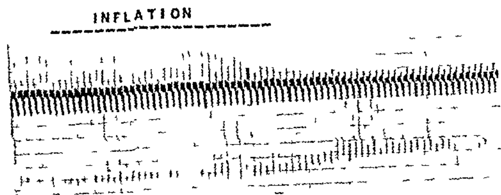


Fig 3 Continuous record of Lead Z during balloon inflation (*stippled line*) following constant obstruction leading to shock Paper speed 5mm /sec (1 second between each solid vertical line) 10 mm = 1 mv Positive deflection = posteriorly negative = anteriorly Both positive and negative Z lead deflections are greatly diminished, and the changes occur during the last part of balloon inflation simultaneously with the right ventricular systolic pressure increment. When the obstruction is stable (from the end of the stippled line on) the ECG is also stable

deflation of the balloon they reverted within 3 to 5 beats This stability and reversibility were found also for the shock state in which the hemodynamic conditions deteriorated continously during the obstruction

In three animals another type of ECG change was observed not included in the presentation till now These changes appeared during severe obstruction after a period in which the common types of ECG changes had been present they were accompanied by widening of the QRS complex, and they reverted more slowly during several minutes These changes were interpreted as right bundle branch block induced by the stretch of the right ventricular wall and were not subjected to further analysis

Relationship between ECG changes and degree of obstruction As described, a progression of the ECG changes was seen from the compensated to the uncompensated state when the group was considered as a whole When all the recordings at different steps of obstruction in the individual animal were considered, this pattern became even clearer From the level where the first ECG changes appeared they always increased progressively with an increasing degree of obstruction and correspondingly subsided with a decreasing obstruction with the same rapid time course as described above Thus in the compensated state there was a relationship between the right ventricular systolic pressure and the ECG changes (Fig 4) When incompensation occurred, this relationship was broken since the pressure then fell with increasing obstruction

Discussion

The results of this study may be summarized as follows

1 An abrupt obstruction of the main pulmonary artery induced definite changes in both QRS and T waves and loops in all dogs

2 In spite of individual differences a characteristic pattern of ECG changes could be defined. In the hemodynamically compensated state this consisted mainly of a counterclockwise rotation of the total QRS complex in the horizontal plane and a superior shift of the T wave

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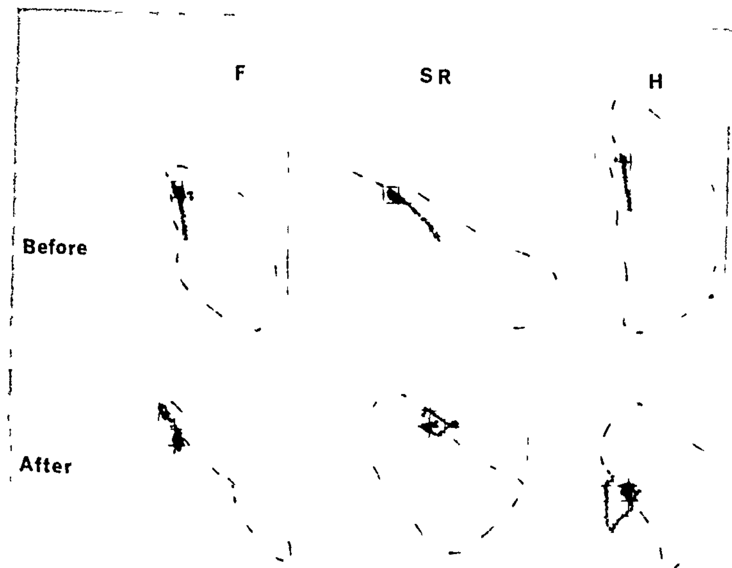


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pulmonary embolism in man[14] There is however some doubt concerning whether stretch alters the action potential[15]

3 The large ST vector seen during shock may represent a current of injury originating in ischemic parts of the ventricles

4 These three factors are all related to the ECG generation In addition the spread of electrical forces to the body surface might also be altered by the increased right ventricular volume the reduced left ventricular volume and the decreased pulmonary blood volume The chamber volumes would be expected to influence the ECG through the so called Brody effect According to this one should expect increased normally oriented and decreased tangentially oriented forces when a heart chamber is dilated.[16,17] The importance of this effect for the ECG pattern in ventricular dilatation has to some degree been empirically confirmed[18,19] but is not supported by the present observations The decrease in anteriorly oriented forces is for instance rather the direct opposite of what would be expected from the Brody effect Recent clinical observations have led to similar conclusions[20]

Some attempts to study ECG changes in animal models of pulmonary embolism have also been made previously[10,11,21] Compared with these the present study has the advantage that closed chest dogs were used and that the ECG was recorded by means of a orthogonal system Most important, each dog could be used as its own control in a series of independent experiments with different degrees of loading

Recently Masood and co workers[22] have given a preliminary report on a study with a similar design They measured axial lead ECG and right ventricular volume before and 30 minutes after acute pulmonary artery balloon obstruction The only significant change in ECG was found to be a leftward and superior shift of the maximal T vector and most of the changes were found at lower levels of obstruction The discrepancies between their work and ours may be caused by different degrees of loading different time intervals and by different recording procedures. Since Masood and colleagues[22] were primarily interested in amplitude changes they may have overlooked the rotation changes for reasons described above

There has been considerable disagreement regarding which ECG changes are typical in pulmonary embolism in man and also regarding the frequency with which these are observed. Since the heart in dog and man electrophysiologically is rather similar[23] the present study may have potential value in the search for more specific and sensitive ECG criteria for the diagnosis of pulmonary embolism in man For instance several workers have searched for various classical ECG signs in pulmonary embolism and have found low incidences of ECG changes This is not astonishing in the light of the present observations since in dogs the typical ECG pattern was found to deviate much from this classical one On the other hand there is considerable agreement between the present findings and those made in the detailed study of Weber and Phillips[24] This agreement applies to the counterclockwise rotation of QRS in the horizontal plane (corresponding to clockwise rotation in the ordinary 12 lead ECG) the increasing terminal QRS vector oriented rightward, posteriorly and superiorly and the dislocation of the septal vector to the left There is also good correspondence with the only reported material of vectorcardiograms during acute pulmonary embolism in man[25] and with a recent report describing left axis shift during pulmonary embolism in man[26] It should be emphasized that the ECG pattern of pulmonary embolism is quite different from that of right ventricular hypertrophy

As described ECG changes rapidly reflected changes in pulmonary artery obstruction Such a correlation between ECG and hemodynamics has also been reported in patients[27] Careful monitoring of the most sensitive ECG parameters could therefore possibly have value in the clinical differentiation between an increasing and a decreasing pulmonary artery obstruction

Summary

Acute pulmonary artery obstruction was induced in 10 dogs by inflating a balloon at the end of a double lumen catheter introduced into the pulmonary artery The ECG was recorded by means of the axial lead system. Significant and generally uniform changes in QRS T and ST segments were observed in all dogs when the

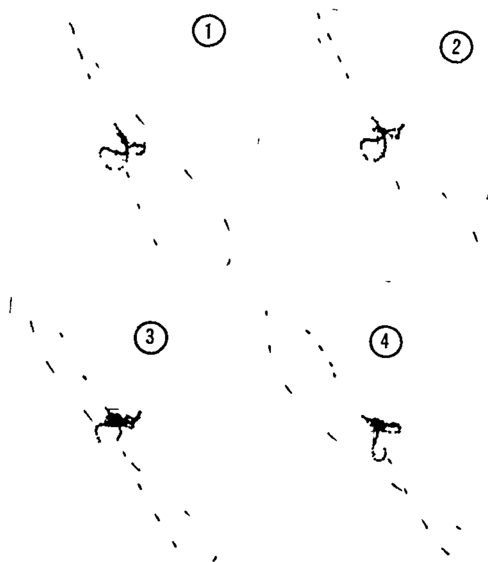


Fig 4 Progressive horizontal plane vector loop changes during increasing right ventricular hypertension in the compensated state This dog was able to maintain higher right ventricular systolic pressures than the others the pressure being 35 76 96 and 122 mm Hg during the recordings ① to ④ The complete QRS loop is slightly but progressively rotated counterclockwise with diminishing anterior forces and increasing forces oriented posteriorly and to the right In addition the middle QRS vectors are dislocated anteriorly and to the right and the T loop is dislocated anteriorly The latter features were characteristic for this animal but were not observed in most of the others

man[12,13] These studies indicate that the right ventricle adapts itself to increasing pulmonary artery obstruction by means of the Frank Starling mechanism—i e with progressive right ventricular dilatation During incompensation other factors such as left ventricular collapse insufficient coronary perfusion, and inversion of the septal bulge probably come into play It is reasonable to interpret the observed ECG changes primarily as a consequence of these factors One major deficiency of this work is therefore that right ventricular volume was not measured In spite of this some possible mechanisms for the genesis of the ECG changes may be mentioned

1 Simple anatomical rotation of the heart may probably explain most of the progressive QRS rotation

2 An acute depression of right ventricular action potentials might explain the dislocation of the QRS forces away from the right ventricle and have recently been described during acute

Case reports

Familial paroxysmal ventricular tachycardia in two sisters

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Numerous types of familial disorders of rhythm or conduction have been reported, including familial types of ventricular tachycardia often presenting with Adams Stokes attacks or sudden death The commonest of these is seen in patients with a long Q T interval with[1] or without[2,3] nerve deafness A much rarer form of paroxysmal ventricular tachycardia is that occurring in children and adolescents with no evidence of heart disease or deafness and with a normal Q T interval[4-6] Two such adolescent sisters were recently admitted to this hospital following attacks of ventricular tachycardia and form the basis of this report

Case report

Case 1 K M a 13 year old white girl presented to this hospital in February 1970 For the preceding week she had had symptoms compatible with an upper respiratory tract infection. On the day of admission, after fairly strenuous exercise she suddenly felt giddy nauseated, short of breath, and developed pain in the right upper quadrant of the abdomen. Her general practitioner noted a pulse rate of 200 per minute and referred her to hospital.

On admission to hospital the tachycardia had abated but she still had an irregular pulse She was slightly overweight, but had no other abnormal features on general examination. Her blood pressure was normal and on examination of the heart a third heart sound was audible There was no evidence of cardiac failure Her hearing was clinically normal Her electrocardiogram (ECG) (Fig 1 upper panel) showed sinus rhythm at a rate of 80 per minute with ventricular extrasystoles a P R interval of 0 13 second, left axis deviation of −45 degrees with some clockwise rotation, with symetrical T wave inversion in Leads V_1 to V_3 T wave flattening in lateral chest leads and a normal Q T interval. The abnormal frontal plane axis persisted throughout her stay in hospital. Chest x ray and full blood count were normal Blood and throat swab specimens cultured in monkey kidney and HeLa cells with one blind passage as well as inoculation into mice proved negative The antistreptolysin O (ASO) titer ranged from 500 to 1 250 Todd units and the erythrocyte sedimentation rate was 30 to 45 mm in the first hour on several readings

Over the ensuing three weeks she remained apyrexial and had no further paroxysms of tachycardia Treatment consisted of bed rest and penicillin. She was thought at this stage to have rheumatic myocarditis in view of the raised antistreptolysin O and elevated ESR which had given rise to probable ventricular tachycardia because of the ventricular extrasystoles seen at the time of admission One month after discharge from hospital on no specific therapy she was seen at follow up and was asymptomatic Physical examination was unchanged and the ECG showed sinus rhythm without any extrasystoles and a normal frontal plane axis. She was advised to resume full activity but one week later following exercise she again developed a tachycardia of 200 per minute She was immediately transferred to hospital by which time she was again in sinus rhythm with frequent ventricular extrasystoles ECG frontal plane axis was now −10 degrees the clockwise rotation was less marked, and left ventricular T waves were now normal (Fig 1 lower panel) Findings were otherwise unchanged. The erythrocyte sedimentation rate ranged from 18 to 44 mm and the antistreptolysin O was still elevated (333 to 833 Todd units) Treatment consisted of a further three weeks of bed rest during which time she had numerous documented attacks of unifocal ventricular tachycardia of varying duration which always subsided spontaneously (Fig 2 upper panel) Various antiarrhythmic drugs were tried singly and in combination during constant ECG monitoring The best combination appeared to be oxyprenolol 20 mg every 6 hours plus quinidine sulfate 200 mg every 8 hours. This regime did not entirely abolish the ventricular extrasystoles but reduced their frequency and no paroxysms of tachycardia occurred.

She was gradually mobilized and allowed to go home with resumption of normal activities over a three month period. She was however advised to refrain from strenuous exertion and competitive sports. Over the next eight months she was

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obstruction reached a level which elevated the right ventricular systolic pressure to above 40 mm Hg The most important changes were a counterclockwise rotation of the total QRS loop in the horizontal plane a large reduction of Lead Z amplitude, and a superior rightward shift of the ST and maximal T vectors The changes appeared within a few beats after balloon inflation, were stable during constant obstruction, and disappeared rapidly when the balloon was deflated

A close relationship was observed between the degree of ECG changes and the degree of pulmonary artery obstruction The type of changes observed corresponded well with those described in man with acute pulmonary embolism

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Case reports

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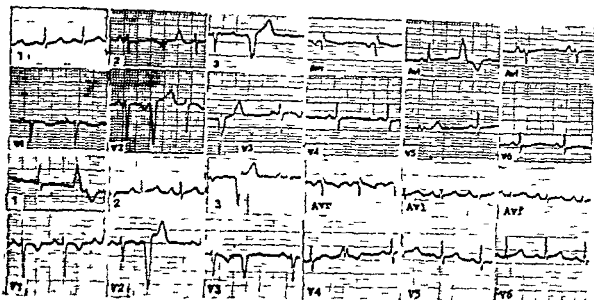


Fig 1 A 12 lead ECG of patient K M immediately after cardioversion from ventricular tachycardia (upper panel) and two months later (lower panel) illustrating change in frontal plane axis Examples from several ECG s done on the same day have been combined in upper panel to illustrate the ventricular extrasystoles which show varying coupling intervals and probable interpolation in Lead V_2

seen at monthly intervals and remained asymptomatic although occasional ventricular extrasystoles were noted at follow up examination

Eight months after her discharge all therapy was stopped and within 24 hours she developed a further attack of tachycardia which had again subsided by the time she reached hospital Treatment was recommenced and she continued to have numerous ventricular extrasystoles. Anti streptolysin O titer was now within normal limits After trial of various drugs both alone and in combination including practolol phenytoin procainamide quinidine and Dibenzyline she was stabilized on a combination of practolol 200 mg and quinidine sulfate 400 mg every 8 hours Sympathomimetic drugs were tried as it had been observed that her extrasystoles were less frequent during spontaneous sinus tachycardia but the use of ephedrine provoked frequent paroxysms of ventricular tachycardia

Over the subsequent year she remained well until January 1972 when she failed to take her tablets and had a recurrence of ventricular tachycardia within 24 hours On admission on this occasion she was sweating and hypotensive with a pulse rate of 265 per minute and a systolic blood pressure of 60 mm Hg The ECG now showed ventricular tachycardia (Fig 2 lower panel) Intravenous practolol 25 mg plus lignocaine 150 mg converted her to sinus rhythm with ventricular extrasystoles and she was subsequently adequately controlled on her previous maintenance dose of practolol and quinidine sulfate It is of interest that the morphology of the QRS complexes during this attack of ventricular tachycardia was totally different from that seen previously (Fig 2)

In the course of her several admissions she had the following investigations the results of which were normal serum and urinary electrolytes serum uric acid serum proteins protein bound iodine blood urea and urinary vanillylmandelic acid Phonocardiogram and echocardiogram of the mitral valve have also been normal The frontal plane axis has been in the pathological left axis range three times more often than it has been found to be normal over the total period of observation On several occasions it has been between 0 degrees and −30 degrees, suggesting incomplete left anterior hemiblock She has now remained asymptomatic for a year since her last attack of ventricular tachycardia while taking her medication regularly

Case 2. M M a 15 year old sister of K M had had no previous significant illnesses but had noted short episodes of irregular rapid palpitations for 4 to 6 months prior to admission These were invariably related to stress and had been confirmed by palpation of the pulse by her mother who by then was aware of the arrhythmic problem of the younger daughter On the day of admission in April 1972 she played a strenuous game of hockey and toward the end of the game felt unduly tired but did not notice palpitations Two hours later she suddenly became acutely short of breath became dizzy sweated, and complained of generalized weakness. Thereafter she had difficulty in recollecting further events and was taken home where her general practitioner was unable to feel her pulse but noted a heart rate in excess of 200 per minute on auscultation

On admission to hospital she was conscious but confused, unable to speak and profoundly shocked. The only palpable pulses were the carotids There was variable intensity of the heart sounds and no recordable blood pressure An ECG showed a ventricular tachycardia at a rate of 265 per minute (Fig 3) Direct current cardioversion using 200 joules, converted her to sinus rhythm with frequent multiform ventricular extrasystoles Intravenous lignocaine at a rate of 100 mg per hour reduced the frequency of the extrasystoles. In view of the known response of her sister to specific antiarrhythmic drugs she was treated with practolol 100 mg every 12 hours plus quinidine sulfate 400 mg every 8 hours. This controlled her extrasystoles almost completely but because

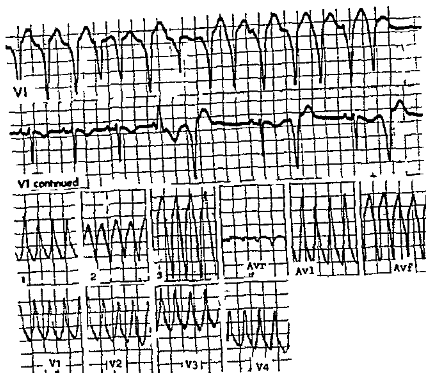


Fig 2. Two examples of ventricular tachycardias seen in patient K M Upper example was paroxysmal and self limited, showing also multiform ventricular extrasystoles. Lower example (10 lead ECG) required conversion with intravenous lignocaine and practolol. (ECG retouched for clarity)

of cinchonism the dose of quinidine had to be halved.

The findings at physical examination when in sinus rhythm, were completely normal and results of the following investigations were also normal full blood count including erythrocyte sedimentation rate antistreptolysin O titer chest x ray serum and urinary electrolytes, serum enzymes protein bound iodine liver function tests fasting free fatty acids, serum and urinary uric acid, creatinine clearance 24 hour urinary cystine and urinary vanillylmandelic acid.

Her subsequent course was uncomplicated apart from transient left axis deviation on ECG immediately after car dioversion which had returned to normal later the following day (Fig 4) Her ECG s were otherwise within normal limits as was the ECG after strenuous effort. Phonocardiogram and echocardiogram of the mitral valve were also normal She has remained well on a combination of practolol 100 mg every 12 hours and quinidine sulfate 200 mg every 8 hours over a nine month follow up period.

Enquiries regarding the family history have revealed that two male first cousins of the father died suddenly and unexpectedly at the age of 18 years. ECG s of both parents and the younger brother aged 11 years were normal Holter ECG monitoring of the brother during periods of activity showed sinus arrhythmia only Q T intervals of the patients, their parents, and their brother were evaluated by the regression formula based on sex age and heart rate derived from Fraser and colleagues[9] and were all normal When assessed by Bazett s formula [10] Q T intervals were not identical but still lay within normal range

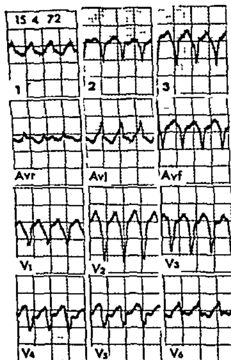


Fig 3 A 12 lead ECG of patient M M showing ventricular tachycardia.

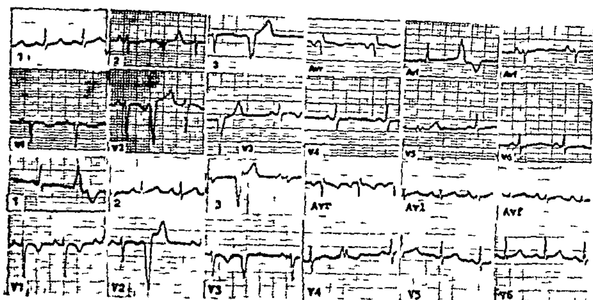


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seen at monthly intervals and remained asymptomatic although occasional ventricular extrasystoles were noted at follow up examination

Eight months after her discharge all therapy was stopped and within 24 hours she developed a further attack of tachycardia which had again subsided by the time she reached hospital Treatment was recommenced and she continued to have numerous ventricular extrasystoles Anti streptolysin O titer was now within normal limits After trial of various drugs both alone and in combination including practolol phenytoin procainamide quinidine and Dibenzyline she was stabilized on a combination of practolol 200 mg and quinidine sulfate 400 mg every 8 hours Sympathomimetic drugs were tried as it had been observed that her extrasystoles were less frequent during spontaneous sinus tachycardia but the use of ephedrine provoked frequent paroxysms of ventricular tachycardia

Over the subsequent year she remained well until January 1972 when she failed to take her tablets and had a recurrence of ventricular tachycardia within 24 hours On admission on this occasion she was sweating and hypotensive with a pulse rate of 265 per minute and a systolic blood pressure of 60 mm Hg The ECG now showed ventricular tachycardia (Fig 2 lower panel) Intravenous practolol 25 mg plus lignocaine 150 mg converted her to sinus rhythm with ventricular extrasystoles and she was subsequently adequately controlled on her previous maintenance dose of practolol and quinidine sulfate It is of interest that the morphology of the QRS complexes during this attack of ventricular tachycardia was totally different from that seen previously (Fig 2)

In the course of her several admissions she had the following investigations the results of which were normal serum and urinary electrolytes serum uric acid serum proteins protein bound iodine blood urea and urinary vanillylmandelic acid Phonocardiogram and echocardiogram of the mitral valve have also been normal The frontal plane axis has been in the pathological left axis range three times more often than it has been found to be normal over the total period of observation On several occasions it has been between 0 degrees and −30 degrees suggesting incomplete left anterior hemiblock She has now remained asymptomatic for a year since her last attack of ventricular tachycardia while taking her medication regularly

Case 2 M M a 15 year old sister of K M had had no previous significant illnesses but had noted short episodes of irregular rapid palpitations for 4 to 6 months prior to admission These were invariably related to stress and had been confirmed by palpation of the pulse by her mother who by then was aware of the arrhythmic problem of the younger daughter On the day of admission in April 1972 she played a strenuous game of hockey and toward the end of the game felt unduly tired but did not notice palpitations Two hours later she suddenly became acutely short of breath became dizzy sweated, and complained of generalized weakness. Thereafter she had difficulty in recollecting further events and was taken home where her general practitioner was unable to feel her pulse but noted a heart rate in excess of 200 per minute on auscultation

On admission to hospital she was conscious but confused unable to speak and profoundly shocked The only palpable pulses were the carotids There was variable intensity of the heart sounds and no recordable blood pressure An ECG showed a ventricular tachycardia at a rate of 265 per minute (Fig 3) Direct current cardioversion using 200 joules converted her to sinus rhythm with frequent multiform ventricular extrasystoles Intravenous lignocaine at a rate of 100 mg per hour reduced the frequency of the extrasystoles In view of the known response of her sister to specific antiarrhythmic drugs she was treated with practolol 100 mg every 12 hours plus quinidine sulfate 400 mg every 8 hours This controlled her extrasystoles almost completely but because

After careful monitoring while on various anti arrhythmic drugs the best combination in our two patients appeared to be quinidine plus a beta blocker Control of extrasystoles has not been perfect however both patients continue to be aware of irregularities of the heart beat especially after exertion but no further episodes of frank ventricular tachycardia have been documented while on therapy Both patients have been exercised to the point of fatigue while on treatment. This produced occasional but gradually diminishing multiform ventricular extrasystoles during the first 10 minutes after exercise without frank ventricular tachycardia Both patients showed reduced postexercise tachycardia due to beta blocker therapy We have found therefore that practolol is an important adjunct to quinidine in the therapy of this condition It does not appear to have the membrane stabilizing quinidine like effect found with propranolol, and its effect in this situation is probably due to its beta blocking property Although this combination of quinidine and practolol has not totally abolished ventricular extrasystoles it appears capable of preventing exercise induced paroxysms of ventricular tachycardia

Gault and colleagues[6] used substantial doses of propranolol with quinidine both singly and in combination without success in treating a 16 year old girl with familial paroxysmal bidirectional ventricular tachycardia and a normal Q T interval. Quinidine sulfate in combination with atrial overdrive suppression pacing was complicated by a paroxysm of ventricular fibrillation and death which they attributed to quinidine toxicity The patient s 18 year old sister with the identical arrhythmia was given quinidine with less frequent but incompletely controlled episodes of arrhythmia She also died suddenly however Green and colleagues[7] reported the cases of three children who died suddenly with this condition and they have since followed up 22 of the family members, all of whom have normal Q T intervals All have done well except the mother who has fainting spells, one of which required cardiorespiratory resuscitation She refused investigation or suppressive therapy and the underlying cause of her collapse remains conjectural She has had, however no further occurrences without medication[17]

Familial paroxysmal ventricular tachycardia without Q T prolongation appears to be a distinct entity about which there have been few reports in the literature Much remains to be learned regarding the natural history and therapy Focal mononuclear cell infiltration of the conducting system in excess of myocardial involvement proper has been reported in a single case of this disorder[8] These pathological changes may or may not have had a genetic background and it is postulated that they may have contributed to continued unsuppressed re entry phenomena and ventricular fibrillation Quinidine may aggravate rather than fully suppress episodes such as these and this may be dose related[18] Beta adrenergic blocking agents and in certain instances carbamazepine have proved useful.[19] In our two cases practolol in combination with quinidine used continuously over 12 and nine months respectively have met with no adverse effects Syncope due to ventricular tachycardia has been prevented but ventricular extrasystoles have not been entirely controlled.

An unexplained aspect of both sisters has been the intermittent left axis deviation due to varying degrees of left anterior hemiblock While bundle branch or fascicular block is a well recognized phenomenon occurring during a tachyarrhythmia due to rate dependent refractoriness of part of the specialized conduction tissue its occurrence following the arrhythmia is not a recognized phenomenon Posttachycardic phenomena of other types are known such as T wave inversion[20] and depression of ventricular contractile state and total energy stores[21] Rosenbaum and co authors[22] report having seen left anterior hemiblock with or without associated right bundle branch block in patients resuscitated from cardiac standstill or ventricular fibrillation and have attributed the conduction disturbance to hypoxia In patient M M left anterior hemiblock was seen in ECG s only one hour and 18 hours after cessation of the ventricular tachycardia, while the axis remained consistently normal thereafter In patient K M however the hemiblock came and went as did the bouts of ventricular tachycardia Although no clear temporal relationship could be established it is possible that the axis was at times affected by clinically undetected bouts of tachyarrhythmia The relationship of the axis shift to the bouts of tachyarrhythmia and its possible mechanism must therefore for the present remain unresolved.

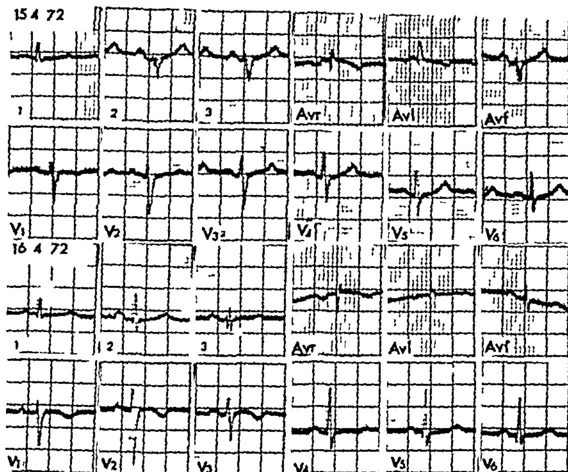


Fig 4 A 12 lead ECG of patient M M immediately after electrical cardioversion showing abnormal left axis deviation (upper panel) which had returned to normal later the following day (lower panel)

Discussion

Paroxysmal ventricular arrhythmias with or without syncope in patients with otherwise normal hearts and a prolonged Q T interval on ECG may occur in families[1-3] or sporadically [11] Such patients with associated deafness were originally described by Jervell and Lange Nielson[1] and until 1971 18 similar cases had been recorded.[11] Romano and colleagues[2] and Ward[3] later described an identical condition in families with normal hearing and 50 such cases have since been documented.[11] The natural history of these prolonged Q T interval syndromes is one of diminishing frequency of syncopal attacks and lessening risk with advancing age This may be related to normalization of the Q T interval with age,[12] with less chance therefore of a ventricular extrasystole occurring on the T wave of the preceding beat, thereby initiating ventricular tachycardia or fibrillation However improvement may occur in the face of persistently prolonged Q T time and in spite of inconsistent therapy

Far less common than the familial ventricular tachycardias with prolonged Q T intervals are those known to occur without evidence of Q T prolongation Only five reports of such families could be found in the literature [4-8] Like the patients with the long Q T syndrome episodes of syncope are often related to exercise or emotional stress [4 5 7] but also occur spontaneously while at rest [5] It is well known that the Q T interval varies with heart rate from person to person and in the same person from day to day It is lengthened by electrolyte disturbances cerebrovascular accidents and certain drugs Frequent measurements of the actual and corrected Q T interval should be made at different times before abnormality can be excluded [9 10] Q T intervals in our patients were measured on numerous occasions both before and after treatment was commenced and were normal on all occasions The Q T intervals of both parents and the younger sibling were also consistently normal There were no familial relationships between this family and those known to have familial ventricular tachycardia with prolonged Q T intervals described from other centers in this country [13 16]

Observations during clinical 2 1 and 3 1 A-V block below the A-V node

Evidence of partial penetration of atrial impulses into the His bundle

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Experimental[1,2] and clinical[3-14] His bundle electrograms (HBE) have demonstrated that the site of block in Mobitz Type II A V block is usually below the A V node While the site of block has been defined, the mechanism of the conduction disturbance remains less clear [3,15] Experimental studies by Watanabe and Dreifus[1,15] defined possible mechanisms of 2 1 Mobitz Type II A V block and higher grades of A V block but thus far confirmation in man through the use of His bundle recordings of the mechanisms demonstrated experimentally has not been described.[15]

The purpose of this report is to illustrate clinical His bundle recordings that demonstrate one mechanism of 2 1 and 3 1 A V block below the A V node During 2 1 block impaired conduction within the His bundle is indicated by alternation of the His potential amplitude and duration while during 3 1 block progressive penetration of the atrial impulse into the His Purkinje system is reflected by the progressively greater amplitude of the His potentials Possible electrophysiologic explanations for these observations are discussed.

Results of His bundle electrograms and atrial pacing

The studies reported below were performed on a 54 year old man with dizziness and dyspnea on exertion A syncopal spell had never occurred. There was no clinical evidence of coronary artery disease The electrocardiogram (ECG) showed right bundle branch block (RBBB) with intermittent 2 1 A V block (not shown) No transition from 1 1 A V conduction to 2 1 A V block was recorded

A HBE was recorded during normal sinus rhythm at a rate of 76 beats per minute One to one A V conduction was present with a normal A H interval (80 msec) a prolonged His potential duration (22 msec) and a prolonged H V interval (80 msec) The QRS complexes displayed a RBBB pattern (Fig 1)

Atrial pacing was begun at a rate of 80 per minute One to one A V conduction continued and all His potentials were of similar amplitude (Fig 2) The atrial rate was then increased to 88 per minute Two to one A V block immediately occurred and the non conducted atrial impulses were followed by His potentials of lower amplitude than the His potentials accompanying the conducted atrial impulses (Fig 3) At this time several pacing stimuli were noted to fail to depolarize the atrium Fig 4 displays one of the three instances recorded when the pacing stimulus failed to produce atrial depolarization A sinus beat occurred creating a cycle length of 920 msec This was followed by a short cycle with a prolonged A H interval and a diminutive His potential. The possible significance of this will be discussed. The pacing catheter was then repositioned and the milliamperage was increased with consistent atrial depolarization

When the atrial rate was increased to 115 per minute two to one A V block persisted and further diminution of amplitude of the non con

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Summary

Two sisters aged 13 and 17 years, who presented with paroxysmal ventricular tachycardia and *intermittent left axis deviation are described* They had otherwise normal hearts with normal Q T intervals, hearing was also clinically normal Satisfactory therapeutic control of paroxysms of ventricular tachycardia was achieved, using a combination of practolol and quinidine although isolated multiform ventricular extrasystoles persisted

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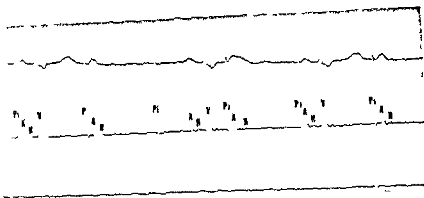


Fig 4 The third pacing stimulus is not conducted to the atrium This is followed by a sinus escape beat The next pacing impulse creates a short atrial cycle length with consequent prolongation of the A H interval and reduction of the His potential amplitude

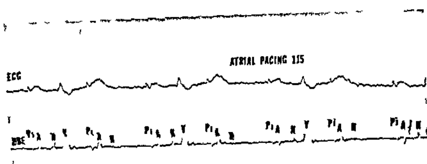


Fig 5 Atrial pacing at 115 per minute 2 1 A V block with further reduction in amplitude of the non conducted His potentials.

catheter was repeatedly checked by fluoroscopy No visible variation was noted. Following completion of the recording at rate 140 per minute the rate was reduced to 100 per minute and the His bundle recording catheter was purposely manipulated in an attempt to find a location where the His potentials were of equal amplitude No such site could be found. Nevertheless, the possibility that the varying amplitude of the His potentials is artifactual as a result of slight changes of catheter position must be considered.

Discussion

Differentiation of the two types of second degree block cannot be made during 2 1 A V block unless a transition to a different degree of block is recorded to permit observation of the behavior of the P R interval. However during 2 1 A V block a Mobitz Type II mechanism is inferred by the presence of bundle branch block in franodal block and a higher grade of block associated with an increased atrial rate [12] Thus *Mobitz Type II* block is probably present in this patient More important to the discussion than the designation of the type of Mobitz block is the clear demonstration that the level of block is below the A V node

Observations during 2 1 A V block

A different degree of penetration of the atrial impulse into the His bundle is suggested by the alternating amplitude of the His potential during 2 1 A V block (Figs 3 and 5) The less deep penetration of the non conducted atrial impulse may be explained on the basis of decremental conduction within the His bundle and/or rate related changes of the refractory period of the His bundle It is not possible with the information available to be certain about the electrophysiologic mechanism However some influence of cycle length on the refractory period

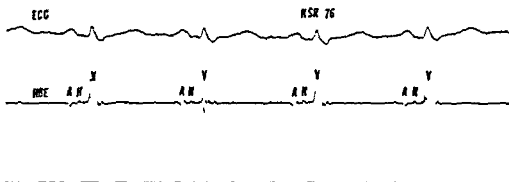


Fig 1 Lead I (top) and HBE (bottom) Sinus rhythm during 1 1 A V conduction RBBB of the QRS complexes A H interval 80 msec H V interval 80 msec His potential duration 22 msec

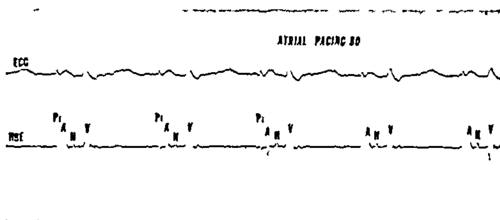


Fig 2 Atrial pacing at 80 per minute 1 1 A V conduction with similar amplitude of each His potential

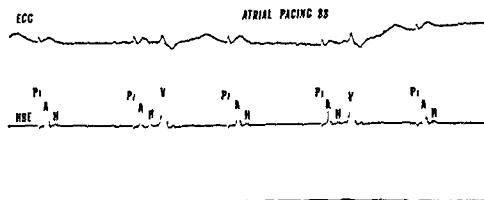


Fig 3 Atrial pacing at 88 per minute 2 1 A V block with reduced amplitude of the non conducted His potentials

ducted His potentials was seen (Fig 5) Finally, at a paced rate of 140 per minute 3 1 A V block occurred The first non conducted atrial impulse was followed by a very low amplitude His potential, the second non conducted impulse was followed by a His potential of greater amplitude, and the third atrial impulse underwent atrioventricular conduction (Fig 6)

It should be noted that during the study the position and stability of the His bundle recording

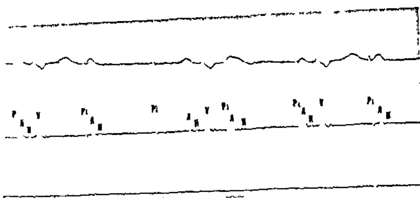


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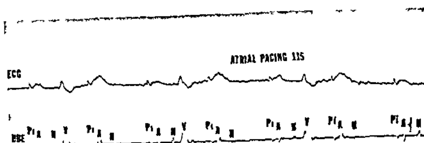


Fig 5 Atrial pacing at 115 per minute 2 1 A V block with further reduction in amplitude of the non conducted His potentials

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Fig 6 Atrial pacing at 140 per minute produces 3 1 A V block with reduced amplitude of the first non conducted His potential greater amplitude of the second non conducted His potential and atrioventricular conduction of the third impulse

and conduction properties of the His bundle is suggested by the occurrence of a diminutive His potential following the atrial impulse that completed a long short cycle sequence (Fig 4) This is akin to the well known tendency of premature supraventricular impulses to undergo impaired conduction (usually within the right bundle branch) when they follow longer R R intervals [16 18] In normal conduction tissue, a premature impulse that successfully traverses the A V node is most likely to undergo conduction delay or block at a distal gate within the right bundle branch [19] *In this instance the impulse encountered* refractoriness and impaired conduction within the His bundle The duration of refractoriness has been shown, in vitro, to be enhanced in tissue displaying impaired conduction [20]

In the absence of recording electrical activity from the more distal portions of the His Purkinje system, it cannot be determined exactly where the impulse is finally blocked However, in view of the very low amplitude His potential seen in Fig 5 it is probable that the impulse encounters progressively refractory tissue within the His bundle and undergoes decremental conduction in that region, similar to the decremental conduction within the canine His Purkinje system of properly timed premature atrial extrasystoles [21] The mechanism of the sustained 2 1 A V block is not certain but the alternation of His potential amplitude and duration is similar to the alternation of action potential duration in the proximal bundle branch seen during 2 1 block at rapid rates of stimulation of the isolated canine distal conduction system [22] The success or failure of A V conduction could be determined by an alternating degree of repolarization within the His Purkinje system

Other mechanisms to account for some instances of Mobitz Type II block have been demonstrated but do not appear applicable here Retrograde concealed conduction into the A V node of a spontaneous junctional extrasystole causing block of the next atrial impulse[23,24] and slight variations of the P P interval resulting in block of a premature impulse within the A V node[2] are excluded by the His bundle recordings

A number of clinical examples of 2 1 block below the A V node have been published [4 7 9 13 14] but only one record (Fig 7, reference 10) shows a varying degree of penetration of the non conducted atrial impulses Thus it appears that in most instances of subnodal 2 1 A V block, conduction through the His bundle proximal to the *recording site* is unimpaired This is consonant with the pathologic studies by Harris and colleagues[25] which indicate that in chronic heart block due to fibrosis of the conduction system the disease process is essentially confined to the bundle branch level with sparing of the His bundle However, if the disease process involved the His bundle as well as the bundle branches then varying degrees of impaired conduction within the His bundle might occur during 2 1 A V block

Observations during 3 1 A V block

In 1948 Langendorf[26] deduced that 3 1 A V block (Fig 2 Lead III) was due to deep penetration of the first non conducted impulse causing

reduced transmission of the succeeding impulse In 1956 Langendorf and Pick[27] again deduced from a clinical ECG (Fig 8*B* of reference 27) that transient 3 1 A V block may be due to either progressively deeper or lesser penetration of the atrial impulses Watanabe and Dreifus[1] subsequently confirmed both patterns of conduction by recording action potentials from two regions of the A V node in the isolated perfused rabbit heart They noted that the pattern of progressively deeper penetration of the atrial impulses occurred more often than the pattern of progressively less deep penetration

Clinical His bundle recordings during 3 1 or higher grades of A V block have generally not shown evidence of varying penetration of the blocked atrial impulses[5] However Berkowitz and associates[10] published a His bundle recording during 4 1 block which shows that the first impulse is blocked below the His bundle while the next two impulses are blocked proximal to the His bundle (Fig 7 of reference 10) In Fig 11*D* of Langendorf and associates[12] four non conducted atrial impulses are followed by His potentials of varying but not progressively greater or lesser amplitude Fig 5*A* in an article by Schuilenberg and Durrer[28] depicts 3 1 A V block with progressively deeper penetration of the two non conducted impulses However this clinical tracing as well as several experimental and clinical records presented by Watanabe and Dreifus[15] demonstrating progressively deeper penetration of atrial impulses during 3 1 A V block reveals both intranodal (Wenckebach) and subnodal block The progressive penetration into the His Purkinje system could be related to the A V nodal conduction delay permitting more time for the distal conduction pathways to recover[29]

During 3 1 A V block in the current case the block was entirely subnodal Several levels of impaired conduction below the A V node are indicated by the RBBB prolonged H V time of the conducted impulses and the progressive penetration of the non conducted impulses into the His tissue It appears that the first non conducted atrial impulse undergoes decremental conduction within the His bundle Conduction of the second impulse is improved—perhaps because of further time for the His bundle to repolarize or because of more synchronous repolarization of His bundle fibers—but is blocked distal to the His bundle recording site Finally the third atrial impulse is conducted to the ventricle although impaired conduction through the His Purkinje system is still apparent in the prolonged His potential duration and H V interval The progressive penetration of the atrial impulse into the His Purkinje system and ultimate ventricular depolarization may be related to the conduction delay within the His bundle allowing time for recovery of a more refractory gate somewhere within the left bundle branch

This clinical tracing (Fig 6) showing progressively deeper penetration of the atrial impulses during 3 1 A V block appears similar to the experimental recordings by Watanabe and Dreifus[1 15] however a difference does exist During their experimental 3 1 block associated with progressively deeper penetration of the atrial impulses the QRS complexes were narrow and the conduction impairment was primarily intranodal[1 15] In this clinical record the QRS complexes are wide (RBBB) and the conduction impairment is entirely subnodal

Summary

A clinical His bundle recording during 2 1 A V block below the A V node displayed RBBB a prolonged H V interval and alternating amplitude and duration of the His potentials The reduced amplitude of the non conducted His potential suggests a lesser depth of penetration into the His tissue with subsequent block The reduced His potential amplitude may be due to decremental conduction within the His bundle and/or prolonged refractoriness of the His tissue following atrioventricular conduction of the preceding atrial impulse

During 3 1 A V block progressively deeper penetration of the atrial impulses into the His Purkinje system occurred. Progressive penetration into the more proximal His Purkinje system may have permitted recovery of a more distal area of refractoriness with subsequent atrioventricular conduction This mechanism appears similar to one of the mechanisms of 3 1 A V block demonstrated experimentally except that in this clinical record the major site of impaired conduction and progressive penetration is within the His Purkinje system rather than within the A V node

I would like to thank Virginia Kanyer for her assistance in the preparation of this manuscript

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Refractory paroxysmal supraventricular tachycardia

Treatment with patient controlled permanent radio frequency atrial pacemaker

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Paroxysmal supraventricular tachycardia is rarely a life threatening disorder except in the presence of other significant cardiac disease Termination of attacks and prevention of subsequent attacks can usually be managed with appropriate antiarrhythmic agents or by avoidance of precipitating causes In an occasional patient however attacks of supraventricular tachycardia may be incapacitating or even life threatening and may present a severe therapeutic challenge if the response to conventional therapy is unsatisfactory

This report concerns a patient in whom conventional therapy failed. Her attacks of supraventricular tachycardia had increased in frequency duration and severity of symptoms and frequent trips to the hospital for DC cardioversion were necessary On one occasion her survival was in doubt Division of the bundle of His with subsequent dependence on permanent ventricular pacing was entertained While this approach was being considered competitive atrial and ventricular pacing were investigated. The solution finally employed was use of a permanently implanted radio frequency coupled artificial atrial pacemaker which could be controlled by the patient to terminate her own attacks This device has worked successfully and the patient has been followed for over fifteen months without serious subsequent problems

This report describes the evaluation of this patient the implantation of the pacing device and the subsequent course and problems during the following year

Case report

B S is a 47 year old housewife As a child, she had a febrile illness with joint pains which was diagnosed as rheumatic fever Ever since she has had paroxysms of rapid heart rate which originally caused little trouble except for dyspnea during the attack and terminated spontaneously She had had five children without complication or difficulty Chest x rays and physical examination during this time remained consistently normal Other past history family history and social history were non-contributory

In 1968 because a heart murmur had been heard for the first time the patient underwent right heart catheterization The right atrial and ventricular pressures were normal and no valvular calcification was seen during fluoroscopy By

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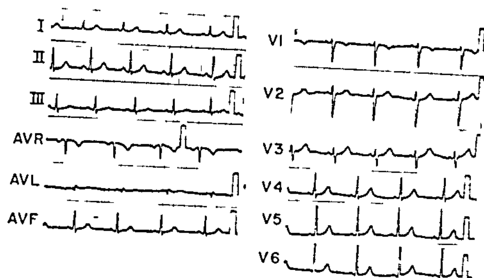


Fig 1 Normal resting electrocardiogram recorded between episodes of supraventricular tachycardia

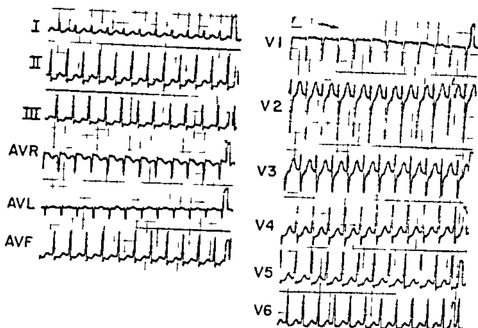


Fig 2 Typical tracing of an episode of supraventricular tachycardia The rhythm is a regular supraventricular tachycardia rate 200 Atrial activity is not evident There is some ST segment displacement likely secondary to the rapid rate

this time the episodes of rapid heart rate had been documented to be paroxysmal atrial tachycardia The frequency of attacks was controlled satisfactorily with quinidine and propranolol

During the next four years the episodes of paroxysmal supraventricular tachycardia became more frequent and incapacitating The patient noticed a steadily decreasing exercise tolerance because exercise appeared to precipitate an attack By late 1971 she claimed that she could not do the dishes from a single meal without an attack of tachycardia Drug therapy at this time included digitalis propranolol quinidine procainamide and diphenylhydantoin individually and in various combinations No combination of these agents appeared effective in preventing attacks In addition the arrhythmia was becoming more difficult to cardiovert with DC shock or carotid massage pressor amines were required on twelve occasions as adjuncts to cardioversion At this time the resting electrocardiogram was normal (Fig 1) between attacks of supraventricular tachycardia (Fig 2)

On November 26 1971 the patient was admitted with a sustained supraventricular tachycardia at a rate of 188 per minute which could not be converted with DC cardioversion and pressor agents in five attempts At this time she was febrile (39 5 C) and had a blood pressure of 80/60 She was slightly cyanotic had cold skin and appeared acutely ill There were bilateral interstitial alveolar infiltrates on the chest x ray (Fig 3) The arterial Po_2 was 44 (patient breathing room air) Pco_2 28 The supraventricular tachycardia was converted to sinus rhythm the next day during an intravenous administration of propranolol The supraventricular tachycardia recurred several times during

that admission, but was converted readily on subsequent occasions with conventional methods (carotid massage) and/or intravenous propranolol Bilateral pleural effusions developed the second hospital day the removed fluid was a nondiagnostic transudate

A papular rash developed approximately two weeks after admission and it was subsequently determined that the patient was allergic to digoxin which was then discontinued The febrile illness was therefore considered a possible hypersensitivity reaction to digitalis

On February 12 1972 approximately seven weeks after discharge from the hospital the patient was admitted with another episode of paroxysmal supraventricular tachycardia which had lasted approximately three hours and had not responded to conventional treatment in the emergency room Over the next three days the cardiac rhythm was converted to sinus rhythm numerous times only to revert to supraventricular tachycardia within a few beats or a few minutes

At this point a temporary transvenous atrial pacemaker catheter was placed in the right atrium The supraventricular tachycardia could be converted to sinus rhythm by means of fixed rate competitive atrial pacing at rates between 60 and 100 Often as long as 15 minutes of competitive atrial pacing was required to convert to rhythm

On February 24 1972 the patient underwent a right thoracotomy during which two atrial electrodes were sutured into the interatrial groove with their proximal end connected to a radio frequency receiving coil and pulse demodulator which was placed in a small subcutaneous pocket beneath the right clavicle A radio frequency impulse generator† provided stimuli which were transmitted from transmitting coil via receiving coil to the atrial electrodes The device was used on numerous occasions during the surgical procedure to terminate usually within a few seconds the attacks of supraventricular tachycardia which occurred

Postoperatively there was nearly continuous supraventricular tachycardia for the next two weeks Each episode could be broken within seconds after onset with the radio frequency pacemaker but the tachyarrhythmia would recur within a few seconds or a few minutes Sustained sinus rhythm was rare It was found that driving the atria continuously at a rate of 130 to 135 would greatly reduce the frequency of attacks of supraventricular tachycardia and this was done for several days Gradually and with increasing doses of propranolol the frequency of supraventricular tachycardia attacks decreased, and the atrial pacemaker was used only when necessary

The postoperative course was further complicated by episodic chest pain and dyspnea about two weeks postoperative A radioisotope lung scan at this time was considered consistent with pulmonary emboli. Anticoagulants were instituted, and the patient had no further similar difficulties



Fig 3 Chest x ray during a severe episode of tachycardia. The cardiac silhouette is borderline enlarged. There are bilateral interstitial alveolar infiltrates compatible with bilateral pulmonary edema

During the year after pacemaker implantation while the patient has been using propranolol the frequency of supraventricular tachycardias has waxed and waned During the first month after implantation supraventricular tachycardia occurred over 200 times After hospital discharge approximately one month after pacemaker implantation there were only rare episodes of supraventricular tachycardia each of which was promptly broken by the patient using her external pacemaker control Beginning approximately six months after discharge the incidence of supraventricular tachycardia has again increased, such that approximately 2 to 3 times weekly the patient breaks her supraventricular tachycardia by driving her atria at 300 per minute Because the patient can break these attacks promptly they cause her little distress During this time heart size has returned to normal and the lungs have remained clear Physical examination has remained consistently negative except for the presence of the pacing device The patient considers her physical condition so much improved that she is now planning to go to work

Discussion

Evaluation of patient and selection of pacemaker type The failure of drug therapy adequately to control this patient s supraventricular tachycardia indicated that a more radical form of intervention was required. It was felt that a surgical section of the bundle of His might be required, with subsequent dependence upon a permanent artificial ventricular pacemaker This approach had the obvious disadvantages of first, necessity of thoracotomy second, irreversibility of the surgically induced AV conduction deficit and permanent dependence upon an artificial

A hypersensitivity reacti n to digoxin was s pported by a pos t ve whe l nd flare rea ti n to intrade m l skin test ng w th a 1 100 d luti n of dig xin Control subjects show d no such ti n. This hypersens t vity reaction could be transferred p ssi ely using the pa t ent s serum, to n rmal controls (Prausn tz Kustner test) Heat ng the pati nt s serum fo 30 min tes t 56 lessened the ab lity of the serum to transfe th ski react on. The autho s are nd bted to Dr Russel Tomar who perform d the hypersens tivity test ng

†Specially designed nd provided by Medtron c I c 3055 Old H gh way Eight, M n eapolis, M nn 55418



Fig 4 The two myocardial type electrodes sutured into place along the interatrial groove on the right side of the heart The junction of the superior vena cava with the right atrium can be seen just above and to the left of the *electrodes The base of the right* auricular appendage is directly above the electrodes

pacemaker for a relatively young woman, and third uncertainty as to the success of the surgical procedure

One possible alternative approach was the use of a synchronous or demand ventricular pacemaker On inactivation of the sensing circuit with an externally placed permanent magnet the pacemaker becomes asynchronous and competitive with the spontaneous ventricular beats This type of approach was first successfully used to terminate the supraventricular tachycardia associated with the Wolff Parkinson White Syndrome [1] and has also been used for paroxysmal supraventricular tachycardia unassociated with Wolff Parkinson White Syndrome [2] To evaluate this approach, a temporary transvenous bipolar pacemaker catheter was inserted into the right ventricular cavity During an attack of supraventricular tachycardia the ventricles were paced competitively asynchronously at rates up to 150 per minute Twenty minutes of such continuous pacing failed to convert the supraventricular tachycardia This approach was therefore discarded

Another alternative considered was the use of an atrial synchronized pacemaker with driving leads attached to the atria At times of supraventricular tachycardia the sensing circuit could be similarly inactivated with an external magnet and the atria paced asynchronously at a fixed rate This approach has been previously used to break re entrant supraventricular tachycardias and atrial flutter [3,6] To evaluate this possibility, the previous transvenous pacing electrode was withdrawn to the right atrium and placed in the right atrial appendage In this electrode location the pacemaker drove and sensed satisfactorily During the next several episodes of supraventricular tachycardia, the atria were paced competitively at fixed rates up to 150 per minute Although competitive atrial pacing usually broke the tachycardia it had the following disadvantages for long term use first, the tachyarrhythmia was often sustained for as long as 15 to 20 minutes before it was interrupted by competitive atrial pacing at these rates second with an atrial pacemaker driving the atria at fixed rate of 150, the patient often could not tell when her arrhythmia had stopped. This presented a problem of patient control of the pacing device a necessity if she were ever to return home and live a relatively normal life This approach also had the disadvantage of requiring a thoracotomy for reliable placement of atrial pacing leads and also the disadvantage of requiring surgery every 18 to 24 months for pulse generator and battery replacement.

The use of an electronic carotid sinus nerve stimulator has been advocated for control of supraventricular arrhythmias [7] This was rejected for this patient because of the great difficulty in breaking her supraventricular tachycardia with ordinary digital carotid massage or with intravenous vasopressor drugs such as phenylephrine

The externally controlled radio frequency coupled carotid sinus nerve stimulator did have certain attractive features One of these is external control for intermittent use by the patient The second desirable feature is the easy replacement of the power source with batteries being purchased by the patient rather than requiring a surgical power source implantation The carotid sinus nerve stimulator has the advantage of radio frequency coupling such that the power source is external to the patient and the batteries can be replaced at will without surgery This is in contrast to the more conventional implanted pacemakers which require surgical battery replacement every 18 to 24 months The external power source did not appear to be a handicap for this application since the operation of the device is designed to be intermittent

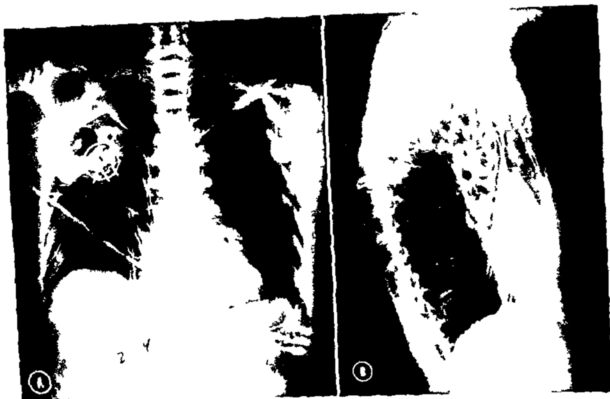


Fig 5 A and B *A* Postero anterior (PA) and *B* lateral chest x rays shortly after implantation of atrial pacing device The heart and lungs are normal The transmitting coil can be seen in the PA view superimposed on the receiving and d modulating unit which is in a subcutaneous infraclavicular pocket The myocardial electrodes are implanted in the interatrial groove

We considered using the impulse generator of the carotid sinus nerve stimulator coupled *via* radio frequency transmission to an implanted receiver with the leads attached directly to the atria At this point the reports of Davidson and colleagues[8] and Dreifus and associates[9] were published in which this approach had been used The manufacturer was familiar with the aims of this approach and was extremely cooperative and helpful in furnishing such a radio frequency coupled stimulator

Surgical implantation The choice of implantation site for the two myocardial type electrodes also presented a problem The furnished electrodes with their insulated lead appeared too stiff and heavy to be secured reliably to the right atrial wall although the report of Davidson and colleagues[8] described their placement on the right auricular appendage We concluded that more secure placement could be achieved along the interatrial groove on the right side of the heart, a site at which there is considerably more substance to the atrial wall (Figs. 4 and 5) The stability of these electrodes and their complete reliability throughout the first 15 months after implantation have been gratifying

Description of pacing device and its use The external pulse generator used by this patient generates pulsatile radio frequency energy at approximately 490 KHz Each pulse is approximately 1 5 msec in duration A variable adjustment controls the rate of stimuli between 50 to 300 pulses per minute During normal use the transmitter coil is placed over the skin separated by skin and subcutaneous tissues approximately 1 cm. from the subcutaneously placed receiving coil. The receiving unit detects and rectifies the pulse modulated radio frequency energy converting these pulses to D C stimuli which are then conducted via myocardial leads to the cardiac electrode implantation site With coil separation of approximately 1 cm the device is said to deliver approximately 20 milliamperes to the heart The pulse generator is equipped with two controls a rate setting with

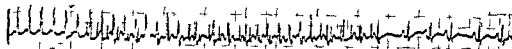


Fig 6 Lead II of the ECG At the beginning of the strip there is supraventricular tachycardia at rate 250 Atrial activity is not evident After 6 spontaneous beats the atrial pacemaker is turned on at rate 305 and captures the atria 1 1 *Transiently the ventricles are driven at rate 300 with increasing PR interval* Midway through the strip an atrial beat is blocked Just before the pacemaker is turned off there is 2 1 AV block with a ventricular rate of approximately 155 When atrial pacing is stopped, sinus rhythm begins at rate approximately 125

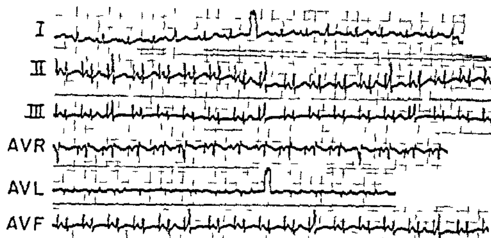


Fig 7 Six limb leads not simultaneous or continuous This was recorded while the atria were being driven continuously at rate 128 in an attempt to overdrive the supraventricular tachycardia There are many examples of delta like waves following atrial pacing stimuli In these beats the atrial stimulus to QRS interval is shorter than on normally conducted beats The T wave *preceding each ' delta like* wave is usually deformed probably containing a premature atrial contraction.

range as described above, and a simple ON OFF switch

When the patient *feels the onset of* supra ventricular tachycardia she places the transmitting coil over her implanted receiving coil She checks the pulse generator rate to make sure it is set at 300 per minute She then depresses the "ON switch, and counts to 5 After 5 seconds, she releases the 'ON' switch This procedure has been successful in several dozen home applications, and has never required a second stimulation during the last 14 months

The usual *operation of the device is shown in* Fig 6 The rhythm strip (Lead II) begins with supraventricular tachycardia at rate 240 per minute The pacemaker then drives the atria at 300 per minute which produces 2 1 AV block *midway through the strip* When pacing is then suddenly stopped, sinus rhythm starts

Other aspects of this patient s supraventricular tachycardia There are several interesting features about the paroxysmal supraventricular *tachycardia* of this patient One unusual finding is the wide range of spontaneous rates at which the tachycardia occurred. Without significant difference in drug therapy, the spontaneous rate varied on different days from 135 to 220 At *times* the ECG pattern was strongly suggestive of atrial flutter, with atrial rate of 300 and 2 1 AV block This wide range of spontaneous supraventricular tachycardia rates suggests that more than one re entrant pathway *was operative in sustaining the supraventricular* tachycardias [10]

There were variations in QRS morphology during tachycardias At times when the atria were being driven by the artificial pacemaker the initial portion of the QRS complex was definitely slurred in ' delta wave' fashion similar to the Wolff Parkinson White disorder (Fig 7) This strongly suggests *the existence of an* AV conduction pathway bypassing the AV node This accessory AV conduction pathway is supported by the initiation of some episodes of supraventricular tachycardia with bizarre aberrant *QRS forms (Fig 8)* which did *not* have the appearance of functional proximal IV bundle delay These bizarre QRS shapes also support AV conduction pathways bypassing the AV node, with the distal end of the bypassing pathway in

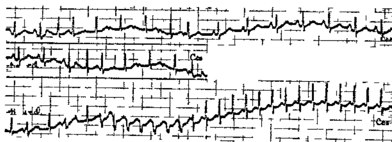


Fig 8 Continuous recording Lead II This rhythm strip demonstrates the onset of an episode of supraventricular tachycardia preceded by premature atrial contractions junctional beats and a run of bizarre QRS complexes which are atypical of proximal IV conduction disorders

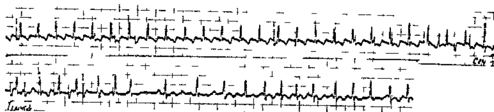


Fig 9 Lead II continuous The atrial rhythm here is probably atrial flutter The atria are paced competitively at 136 per minute The atrial flutter breaks at the beginning of the second strip There is probably a single sinus beat followed by transient atrial fibrillation during which the ventricular response is irregular and averages 140 per minute

itiating ventricular activation in an area other than the distal AV bundle or common bundle of His

Another interesting occurrence during this patient s course was the apparent production of atrial fibrillation when atrial flutter was competitively paced at rate 136 The atrial fibrillation was transient and did not last longer than 10 seconds The patient was not receiving digitalis at this time yet the ventricular response averaged only 140 per minute (Fig 9) This is slower than almost any supraventricular tachycardia that she had

Another feature of this patient s course is that, on one occasion when her atria were paced at 280 per minute her ventricles briefly followed this atrial rate with 1 1 response (Fig 6) This represents an atrial to ventricular pathway functional refractory period less than 220 msec — an unusually fast AV conduction system recovery time [11]

Driving the atria at rates slower than the AV conduction capability often did *not* break the supraventricular tachycardia As with Davidson and colleagues'[8] case the most certain means of breaking the tachycardia was to drive the atria sufficiently fast so that AV block was produced. This is demonstrated in Fig 10 driving the atria at 220 per minute produced 1 1 AV conduction and did not terminate the tachycardia When the atrial rate was 250 per minute second degree AV block with Wenckebach s phenomenon was produced and sinus rhythm (and junctional rhythm) followed the discontinuation of pacing

Follow up

There has been one problem with the R F pacemaker About 11 months after implantation the stimuli became painful to the patient When the transmitting coil was held on the skin over the receiver (coils separated by approximately 1 cm) the pacing stimuli recorded in Lead II were considerably larger than previously When the transmitting coil was lifted off the skin and gradually held further from the receiving coil the recorded stimuli grew progressively weaker until the atria were no longer captured by the pacemaker at a coil separation of 7 5 cm With a coil separation of approximately 6 0 cm the stimuli were the same size as was originally recorded from the device and drove the atria (Fig 11)

The cause of this unusual behavior of the system was not evident The original external pulse generator and antenna were replaced with



Fig 10 Lead II When the atria are driven at 220 per minute there is 1 1 AV conduction Without pacing the supraventricular tachycardia persists at a rate of approximately 205 When the atria are driven at 250 per minute there is second degree AV block with Wenckebach s phenomenon and the supraventricular tachycar dia is broken With slowing of the atrial pacer sinus rhythm and junctional rhythm begin

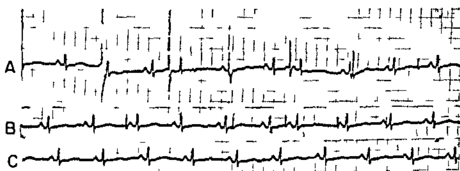


Fig 11 A through C Lead II During the top strip *A* the transmitter coil is initially held on the skin and is slowly removed. By the end of the strip the transmitting and receiving coils are separated by about 10 cm and atrial drive fails Note the large size of the stimulus artifacts while the two coils are separated only by skin and subcutaneous tissue During the second strip *B* the transmitter coil is held approximately 6 cm away from the skin Pacemaker stimuli are approximately the same size as one year previous when the coil had been placed on the skin Each pacemaker stimulus drives the atria except when the atria are refractory The lower strip *C* was recorded with the coils separated by about 15 cm No artificial pacemaker activity is evident

new ones, which have since driven the original receiver and demodulator satisfactorily

Careful examination by the manufacturer of the original transmitter and antenna assemblies revealed no defects or failure modes to account for the unusually large stimulus artifacts Subse quent use of the same transmitter-antenna system by the manufacturer failed to reproduce the problem

The successful use of the implanted pacing device for over 15 months exceeds the life span of similar devices[8,9] previously reported David son and colleagues [8] implant was removed after about one year, as reported by Perryman and Sealy [12] This implant therefore represents the longest successful application of an R F coupled atrial pacemaker for control of supraventricular tachycardia

Summary

A patient with incapacitating recurrent supraventricular tachycardia refractory to medical management, was evaluated for possible surgical intervention Several types of competitive artificial pacemakers were considered as was surgical section of the His bundle plus conventional pacing The patient was treated with a competitive radio frequency coupled atrial pacemaker which she herself operates to break her supraventricular tachycardias The device has operated successfully on numerous occasions for over 15 months Several other aspects of this patient s arrhythmias were discussed

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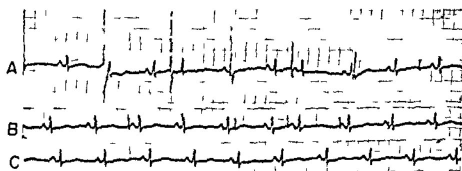


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shows marked posterior displacement of the left ventricle and a significantly bowed right coronary artery indicating an enlarged right ventricle There is also prominence of the right conal branch which seems to wrap around a markedly dilated right ventricular outflow tract This finding is consistent with atrial septal defect

DR MARIN GARCIA As a result of the studies presented, a diagnosis of atrial septal defect with left to right shunt was made

Cardiac failure persisted despite intensive medical management and surgical closure of the atrial septal defect was advised. At operation a secundum type of atrial defect was found measuring about 2 cm in diameter This was closed by continuous sutures Following operation the patient failed to improve and remained in cardiac failure In an attempt to explain this state the possibility of existent myocardial disease was considered

A second right sided cardiac catheterization (Table I) was performed to determine the reasons for persistent cardiac failure The catheter followed a normal course through the right side of the heart The right ventricular pressures were lower than those prior to operation The pulmonary arterial and right ventricular systolic pressures were identical The evident fall in right ventricular pressure was interpreted as a manifestation of maturation of the pulmonary arterial bed. A reading of pulmonary arterial wedge pressure was not obtained

In its levophase the pulmonary arteriogram showed very poor concentration of contrast material but showed a left to right shunt at the atrial level

A second operation was performed. Most of the previous suture line was intact but at the most anterior aspect of the previous repair suture material had torn loose and required resuturing The left atrium was not explored

Following the second operation the patient s course was rather stormy and it was only after a prolonged period of four weeks of hospitalization that she could be discharged with fairly well controlled congestive cardiac failure

One week following discharge the patient was readmitted with severe cardiac failure and died a few hours later

Dr Moller will you please present the differential diagnosis?

DR. JAMES H MOLLER This baby was seen for the first time at the age of three months in severe cardiac failure In this age group ventricular septal defect whether isolated or associated with other conditions such as a patent ductus arteriosus is the most frequent cause of cardiac failure [1] Coarctation of the aorta complete atrio ventricular canal complete transposition of the great vessels myocarditis and endocardial fibroelastosis are other less frequent causes of cardiac failure at this age

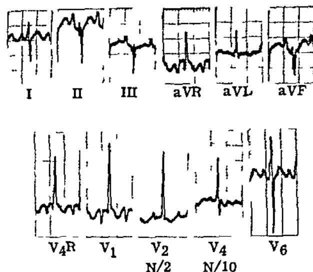


Fig 1 Electrocardiogram of 7 month old girl with atrial septal defect and signs of right ventricular hypertrophy There is a mean QRS axis of −90 degrees in the frontal plane

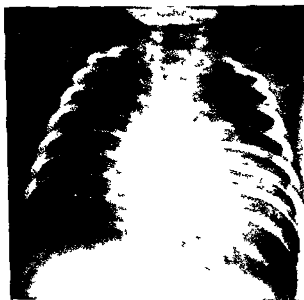


Fig 2 Thoracic roentgenogram in frontal view

Clinical pathologic conference

Jose Marin Garcia M D
Kurt Amplatz, M D
James H Moller, M D
Rajendra Tandon, M D
Jesse E Edwards M D
St Paul, Minn.

DR JOSE MARIN GARCIA This 7 month old girl had been born following a normal pregnancy, labor, and delivery At birth she weighed five pounds 14 ounces While appearing normal in the neonatal period, grunting respirations irritability, and anorexia developed at six weeks of age

These symptoms increased in severity and at the age of three months she was admitted to the University of Minnesota Hospitals because of cyanosis and congestive cardiac failure

Physical examination revealed a tachypneic pale, dusky irritable infant. The cardiac rate was 200 per minute and the respiratory rate was 80 per minute Simultaneous flush blood pressures in the right arm and right leg were each 80 mm Hg Examination of the thorax showed an increased anteroposterior diameter The lungs were clear on percussion and auscultation The precordium was hyperkinetic and the heart was moderately enlarged The first and second sounds appeared normal A Grade IV/VI, precordial, systolic murmur was maximal at the left sternal border Also a diastolic, rumbling murmur was heard at the lower left sternal border The liver was palpable 6 cm below the right costal margin

The hemoglobin was 12 4 grams per cent and the leukocyte count 10 500 per cubic mm

An electrocardiogram (Fig 1) showed a mean QRS axis of 90 degrees in the frontal plane Signs of right ventricular hypertrophy were present The P waves were interpreted as showing signs both of right and left atrial enlargement

The patient was given a digitalis preparation and diuretics and placed in an oxygen tent The congestive cardiac failure responded only partially

Five days after admission, the patient underwent right sided cardiac catheterization (Table I) The course of the catheter was abnormal in that it could be advanced through a low positioned atrial septal defect into the left ventricle There was a left to right shunt of 88 per cent at the atrial level The oxygen saturation of pulmonary venous samples was 92 per cent This was interpreted as consistent with the presence of mild coexistent pulmonary disease The atrial pressures were similar and there was a small gradient (4 mm) between the left atrial and left ventricular end diastolic pressures Because the catheter was not advanced into the pulmonary artery during this study, pulmonary vascular resistance could not be calculated.

Dr Amplatz would you please present the radiologic observations in this patient?

DR KURT AMPLATZ Standard thoracic roentgenograms show generalized cardiomegaly and prominent pulmonary vasculature (Fig 2) As part of the first cardiac catheterization left ventriculography was performed This shows a normal outflow area and absence of significant mitral regurgitation (Fig 3) The clear identification of a ventricular septum which is intact, excludes both single ventricle and ventricular septal defect The normal configuration of the left ventricle excludes persistent common atrioventricular canal The origin of the aorta is normal and there are no signs either of aortic stenosis or coarctation of the aorta

The lateral view of the angiocardiogram

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Fig 4 ■ Accessory left atrial chamber (A L A) viewed from above The probe lies in the opening in the diaphragm which leads from this chamber to the true left atrium below and out of view Endocardium of the accessory chamber is thickened and its wall is hypertrophied. b Left ventricle (L V) and true left atrial chamber (L A) The ostium (between *upper arrows*) in the diaphragm leads from the accessory left atrial chamber (A L A) Upon the anterior leaflet of the mitral valve is a jet lesion (between *lower arrows*) considered secondary to the impact of blood flowing through the opening in the diaphragm and striking this area Ap = left atrial appendage

as an explanation of the systolic murmur a functional tricuspid insufficiency secondary to an obstructive left sided lesion

The electrocardiogram (Fig 1) has unusual features for an isolated ventricular septal defect The mean QRS axis at the frontal plane shows left axis deviation suggesting a ventricular septal defect of the endocardial cushion type however the presence of clockwise rotation of the QRS loop in the frontal plane is against an atrioventricular canal It is difficult for me to relate this electrocardiogram to the clinical findings except to say that the degree of right ventricular hypertrophy indicates an important elevation of right ventricular systolic pressure

Other conditions present left axis deviation such as tricuspid atresia but the precordial lead pattern of right ventricular hypertrophy does not fit well with this diagnosis Single ventricle with high pulmonary flow may also be associated with such an electrocardiographic pattern and may cause cardiac failure early in life The roentgenographic findings (Fig 2) are compatible with a large shunt. Clinically I believe this child to have a ventricular septal defect but cannot fit the electrocardiographic findings into this diagnosis yet I cannot come up with an alternate diagnosis

The catheterization data showed a very large shunt at the atrial level This magnitude of left to right shunt is unusual in isolated atrial septal defect so that a coexistent condition limiting flow into the left ventricle may be present This could be either an anatomic lesion such as mitral stenosis or a disease affecting left ventricular compliance The pressure data show a small diastolic gradient between the left atrium and left ventricle In the presence of an atrial septal defect, pressure characteristics of an obstruction between the left atrium and left ventricle may be masked[23] No significant gradient was found at the mitral valve but it is to be emphasized that simultaneous left atrial and left ventricular pressures had not been obtained

The elevated right ventricular pressure was secondary to high pulmonary flow probably in association with a higher than normal pulmonary vascular resistance though no information is available regarding this state

No condition altering left ventricular compliance could be found on left ventriculogram This study showed an enlarged left ventricle but



Fig 3 a and b Left ventriculograms a Frontal view b Lateral view

Table 1 Synopsis of catheterization data

Site	*First catheterization*		*Second catheterization*	
	Oxygen saturation (%)	*Pressure (mm. Hg)*	*Oxygen saturation (%)*	*Pressure (mm. Hg)*
Superior vena cava	50		38	
Inferior vena cava	82		79	
Right atrium	87	a = 12 v = 7 (5)†	79	a = 7 v = 9 (5)
Right ventricle	87	85/0 10	79	40/0
Pulmonary artery			81	36/20 (28)
Right upper pulmonary vein	92	a = 16 v = 19 (7)		
Left atrium		a = 17 v = 13 (7)		
Left ventricle	91	90/0 13		
Brachial artery				105/65 (80)
Left to right shunt	88 per cent		80 per cent	

Abbreviations a = atrial v = ventricular
† Figures in parentheses indicate mean pressure

The systolic murmur described was apparently pansystolic with maximal intensity at the lower left sternal border and a rumbling diastolic murmur was present at the same area

These findings could be explained by a left to right shunt at the ventricular level with high flow across the mitral valve In the presence of cardiac failure however one could not exclude

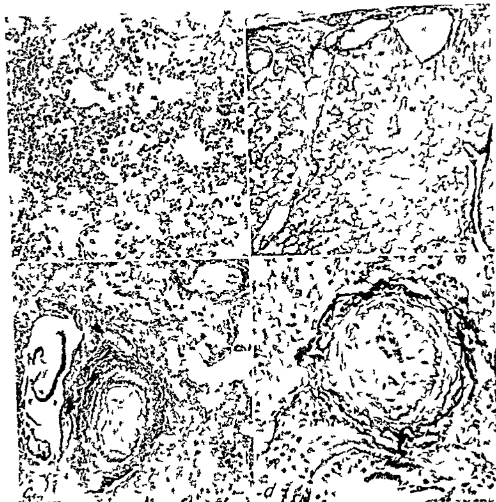


Fig 7 a through d Photomicrographs of lung a Alveolar congestion. Phagocytes and edema fluid are present in alveolar spaces (Hematoxylin and eosin Original magnification × 100) b Dilatation of pleural (*above*) and intrapulmonary lymphatics The picture is consistent with that seen in pulmonary venous hypertension. (Hematoxylin and eosin Original magnification × 24) c Associated with a bronchus (*left side of illustration*) is a muscular artery which shows medial hypertrophy A smaller artery in the right upper part of the illustration shows medial hypertrophy (Hematoxylin and eosin. Original magnification × 80) d A muscular artery shows medial hypertrophy and intimal fibrous proliferation. (Hematoxylin and eosin. Original magnification × 230)

ring was approximately 0 8 cm The mitral valve was normally formed however the atrial surface of the anterior mitral leaflet and the adjoining part of the atrial wall showed endocardial thickening This was considered to be a jet lesion resulting from the impact of the blood entering from the narrow opening in the diaphragm (Fig 4b)

Histologically the diaphragm between the two left atrial chambers was composed of cardiac muscle and covered by endocardium (Fig 5)

The site of the surgically closed atrial septal defect was indicated by the suture line which was almost completely endothelialized except at the most anterior end (Fig 6) From the left side of the septum it was not possible to determine the site of interatrial communication because of complete endothelialization Transillumination of the atrial septum showed that the suture line corresponded with the part of the atrial septum lying between the accessory chamber and the right atrium Thus the communication between the left and right atria had been present between the accessory left atrial chamber and the right atrium.

The remainder of the heart showed no other anomalies. The right atrium and the right ventricle were dilated There was significant hypertrophy of the right ventricular wall The wall thickness of each ventricle was 6 mm The left

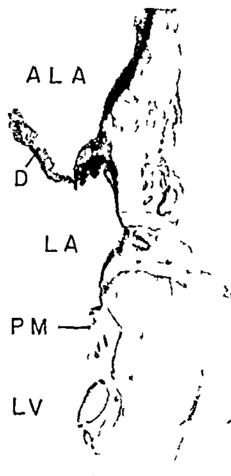


Fig 5 Low power photomicrograph of a section made through the accessory left atrial chamber (A L A) the true left atrial chamber (L. A) the posterior leaflet of the mitral valve (P M) and the left ventricle (L. V) Between the accessory left atrial chamber and the left atrium is the diaphragm (D) which separates the two left atrial chambers The diaphragm is composed of cardiac muscle and covered by endocardium The wall of the accessory left atrial chamber is thicker than that of the true left atrium The mitral valve is normal (Elastic tissue stain Original magnification × 3)

ruled out any significant mitral regurgitation as well as a goose neck deformity of the outflow tract The thoracic aorta and aortic valve appeared normal

At the operation a large atrial septal defect of ostium secundum type was closed and no other cardiac lesions were identified On the basis of the large left to right shunt at the atrial level, one should have considered the possibility of an obstructive lesion above or at the level of the mitral valve

Because the patient failed to achieve improvement, a second cardiac catheterization was performed seeking another anomaly Pulmonary arterial and right ventricular pressures were nearly normal but a significant left to right shunt was present A wedge pulmonary pressure



Fig 6 Right atrium (R A) and right ventricle (R V) In the right atrium is the suture line (between arrows) of the closed atrial septal defect The right ventricular wall is markedly hypertrophied

was not obtained Because the pulmonary arteriogram poorly opacified the left side of the heart, the details of the left atrium were not visualized I would conclude that this child had more than a simple atrial septal defect and that a coexistent obstructive condition either of the mitral valve or left atrium was present

DR MARIN GARCIA Dr Tandon would you please describe the pathologic findings?

DR RAJENDRA TANDON At necropsy the important finding was cor triatriatum A thick muscular diaphragm divided the left atrium into an upper accessory chamber and a lower true left atrial chamber The accessory chamber was spherical in shape and was about 3 cm wide It received each of the pulmonary veins The accessory chamber communicated with the lower chamber through a 5 by 3 mm eccentrically placed opening in the aforementioned diaphragm The opening was located in the anteromedial region and was bounded medially by the septal wall of the atrium (Fig 4a) The anterior, lateral and posterior walls of the opening were formed by the diaphragm The true left atrial cavity, from which the atrial appendage arose was much smaller than the accessory chamber The vertical distance between the lower surface of the diaphragm and the mitral

three cases the foramen ovale presented against both left atrial chambers

In most of the cases with patent foramen ovale described by Niwayama[4] it is assumed that this condition represented a potential opening rather than a through and through defect as was present in the case here discussed as true atrial septal defects appear to be uncommon in cor triatriatum

When in cor triatriatum a defect is present in the atrial septum the dynamics depend upon which of the two left atrial chambers is in communication with the right atrium When the defect is between the accessory left atrium and the right, the defect lies proximal to the obstruction in the membrane between the two left atria The dynamics are like those in the so called Lutembacher syndrome in which atrial septal defect and mitral stenosis are associated The obstruction distal to the defect would favor a greater left to right shunt than when the defect was located beyond the obstructing membrane

The latter situation would yield features like those of mitral stenosis In addition there would be features of left to right or right to left shunt through the defect distal to the obstruction The direction of shunt would depend on the severity of obstruction in the diaphragm and the resulting pulmonary arterial right ventricular and right atrial hypertension

When an atrial septal defect is associated with obstruction to egress of blood from the left atrium, there is always the danger of focusing attention only on the defect. This appeared to have been the situation in the present case

It is appropriate to consider a complicated situation when in an infant, an atrial septal defect is identified. In a current study on infants dying with atrial septal defect Dr Tandon and I have not found any cases in which the defect was the only condition present In each there was an associated, more complex condition

In the case presented, closure of the atrial septal defect removed an escape valve and served to make the obstructive lesion more significant than it had been prior to closure of the defect Evidence for pulmonary venous obstruction is clear in the description of the lungs given by Dr Tandon With these thoughts in mind, it is peculiar that the postoperative right ventricular pressure was recorded as being lower than the preoperative pressure

FINAL DIAGNOSIS Cor triatriatum and atrial septal defect

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ventricular cavity, though normal in size, was much smaller than that of the right ventricle The tricuspid, pulmonary, and aortic valves were normally formed. The pulmonary trunk was dilated The external diameter of the pulmonary trunk was 1 6 cm compared to that of the aorta which measured 1 0 cm

Histologic examination of the right and left ventricular myocardium gave normal results The lungs showed extensive pulmonary edema and features of pulmonary venous and arterial hypertension (Fig 7) The pulmonary veins showed a thick, muscular media bounded by internal and external elastic laminae The pulmonary arteries showed medial hypertrophy and, in many cellular intimal proliferation was also present The arterioles showed marked medial hypertrophy with very narrow lumens The lymphatic channels were dilated The parenchyma showed thickening of alveolar septa, intra alveolar fibrinous fluid consistent with pulmonary edema and numerous pigmented macrophages (Fig 7)

In essence, this patient exhibited cor triatriatum and a surgically closed communication between the accessory left atrial chamber and the right atrium

DR MARIN GARCIA Thank you Dr Tandon I should like Dr Edwards to remark about this case

DR JESSE E EDWARDS The case described is classical for cor triatriatum in which the pulmonary veins join an accessory chamber while the 'true' left atrium lies inferior to this chamber and communicates with the left atrial appendage and the mitral valve

While the developmental explanation for this malformation is subject to continuing debate it is commonly accepted as resulting from faulty moulding of the pulmonary veins with the left atrium

The original connection of the developing pulmonary veins with the heart is through a protrusion toward the developing lungs of that part of the sinoatrial region of the heart which is to become part of the left atrium Later this protrusion the common pulmonary vein is lost as a distinctive structure as it becomes incorporated into the left atrium The ultimate effect of this incorporation is that in the definitive situation each pulmonary vein joins the left atrium directly Faulty moulding of the common pulmonary veins into the left atrium leaves the common pulmonary vein as an identifiable structure, the accessory left atrium

There is variation in the state of communication between the accessory left atrial chamber and the true left atrium Rarely, there is no opening in which case return of pulmonary venous blood is through anomalous collateral channels either into systemic veins or the right atrium [4]

Most commonly there is a communication often single, uncommonly multiple [4] The primary effect upon the circulation depends upon the caliber of the communication between the two left atrial chambers When this is narrow, a functional state like that in mitral stenosis or other forms of pulmonary venous obstruction follows [5] Only unusually is cor triatriatum associated with anomalous pulmonary venous connection [6]

It will be recalled in the case here discussed that a defect had been present between the right atrium and the accessory left atrial chamber On theoretical grounds the foramen ovale should present into the true left atrial chamber but this is not always the case Van Praagh and Corsini[7] suggested that the formation of the underlying pulmonary venous anomaly may be associated with abnormality in the atrial septum These authors indicate that the foramen ovale is often poorly defined and that when a defect is present between the right atrium and accessory left atrial chamber, it represents a form of anomalous pulmonary venous connection to the right atrium That this may be true in some cases at least, is supported by our observations in a case of cor triatriatum in which the foramen ovale was easily identifiable and distinct from the defect between the two sides [8]

While there is still uncertainty about some such defects, it is a fact that a defect may be present between the right atrium on one hand, and either the upper or lower left atrial chamber on the other

Niwayama[4] reviewed the position of the foramen ovale with respect to the left atrial chamber in 25 reported cases of cor triatriatum In 16 cases, the foramen ovale lay between the true left atrium and the right atrium. In 12 of these, it was patent and in four it was sealed In six cases, the foramen ovale presented against the accessory left atrium and was patent in two In

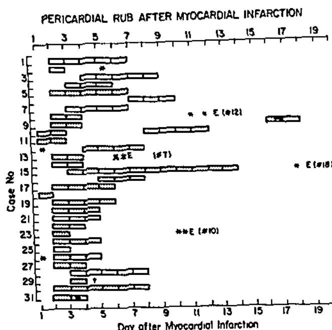


Fig 1 Summary of 31 patients with pericarditis following myocardial infarction Cross hatched bar = anterior wall myocardial infarction clear bar = inferior wall myocardial infarction = ventricular tachycardia = ventricular fibrillation + = atrial fibrillation ++ = paroxysmal atrial tachycardia E = expired (#) = day patient died following myocardial infarction

by at least two observers Although typical pericardial pain was present in most of these patients it alone was not considered a diagnostic criteria

The following classification was used for the evaluation of congestive heart failure

Grade 0 — No sign of congestive heart failure

Grade I — Sinus tachycardia greater than 100 per minute associated with S_3 or S_4 gallop Chest x ray shows increased vasculature in superior lung fields Patient may or may not have dyspnea

Grade II — In addition to signs of Grade I patient has mild to moderate dyspnea and moist rales at one or both lung bases Chest x ray shows hilar congestion

Grade III — Patient with severe dyspnea and clinical and radiographic signs of pulmonary edema

Results (Fig 1)

Incidence Pericarditis was diagnosed in 31 of 305 patients (10 1 per cent) within one week after acute myocardial infarction In the pericarditis group there were 26 men and 5 women with an average age of 62 years while in the control group there were 211 men and 63 women with an average age of 63 years

Location of infarction Twenty patients with pericarditis had an anterior wall infarction and 11 had inferior wall infarction Pericarditis was not seen in any patients with subendocardial infarction In the control group the number of inferior and anterior infarctions were almost equal with 116 anterior and 101 inferior wall infarctions In the control group there were 22 with combined anterior and inferior wall infarctions and 35 subendocardial infarctions (Table I)

Incidence of ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) Five of 31 (16 1 per cent) patients (patients No 2 12 13 26 and 31) with pericarditis developed significant ventricular arrhythmias within the first week The ventricular arrhythmias were not temporally related to the clinical pericarditis in four of five patients In the control group of 274 patients 33 (12 per cent) developed significant ventricular arrhythmias during the first week This difference is not statistically significant ($p > 0\ 50$)

Fundamentals of clinical cardiology

Pericarditis complicating acute myocardial infarction Incidence of complications and significance of electrocardiogram on admission

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Pericarditis is a common, early complication following acute myocardial infarction [1] Baumler[2] is given credit for first describing this entity in 1872 Kernig[3] emphasized the relationship to coronary occlusion and Sternberg[4] suggested the name pericarditis epistenocardica "

With the advent of coronary care units pericarditis has been noted with increasing frequency In spite of this increased recognition, several questions still remain It is the purpose of this study to determine if pericarditis alters the mortality or incidence of significant arrhythmias following acute myocardial infarction The predictive value of the ST segment elevation at the time of admission and the relationship of this complication to Dressler s syndrome is also discussed

Methods

Data were obtained on 305 consecutive patients admitted to a coronary care unit during the period July 1970 through July 1972 The diagnosis of acute myocardial infarction was based on (1) presence of ischemic chest pain (2) typical serial electrocardiographic changes and (3) elevation of serum glutamic oxaloacetic transaminase, serum lactic dehydrogenase, and creatinine phosphokinase Infarctions were classified as transmural if a pathologic Q wave was noted and as subendocardial if characteristic ST and T wave abnormalities occurred[5]

The patients all had constant electrocardiographic monitoring for an average of five days The standard electrocardiogram was recorded daily or more often if indicated clinically Vectorcardiograms were performed in many of the cases to confirm the diagnosis of myocardial infarction ST segment elevation was measured on the day of myocardial infarction and in all cases preceded the onset of pericardial rub The ST segment was measured in the lead showing the greatest amount of elevation which was usually Lead III with inferior wall infarction and Lead V_2 or V_3 in anterior wall infarction Two patients with true posterior wall infarction and pericarditis were excluded from this part of the study A portable chest x ray was taken at the time of admission and was repeated if indicated

The routine of coronary care included constant infusion of lidocaine 2 mg per minute unless there was evidence of A V block or sinus bradycardia Heparin 75 mg intravenously every 6 hours was given unless there was a history of recent gastrointestinal bleeding active peptic ulcer, significant hypertension or other hemorrhagic abnormalities Heparin was usually continued for 3 weeks and was not discontinued if a pericardial rub developed within the first week of myocardial infarction

Pericarditis was diagnosed only by the presence of a typical pericardial rub that was heard

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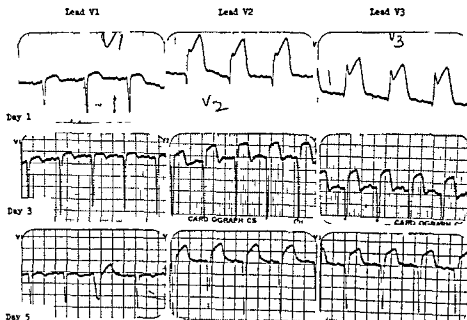


Fig 2 Summary of electrocardiograms on patient No 16 with acute anterior wall myocardial infarction. The marked ST segment elevation had returned toward normal on day 5 at which time the pericardial rub was first heard.

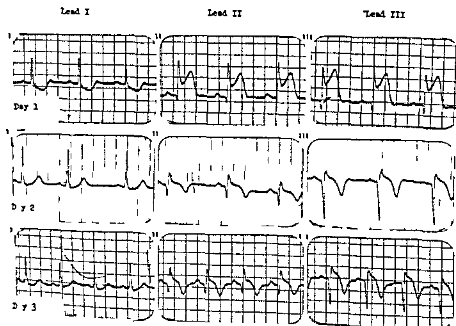


Fig 3 Summary of electrocardiograms on patient No 4 with acute inferior wall myocardial infarction. The pericardial rub was first heard on day 3 at which time the ST segment had returned toward normal.

wall infarction It is assumed that a friction rub generated by a localized area of inflammation either inferiorly or posteriorly could have easily been missed by the examiner

The incidence of pericarditis as an early complication of acute myocardial infarction varies from 6 8 per cent to 42 per cent [12,13] Our incidence of 10 1 per cent is similar to that found by Wood.[14] The wide variation in incidence is largely a matter of how pericarditis is defined,

Table I Site of myocardial infarction

	Pericarditis	*Control*
Anterior wall	20	116
Inferior wall	11	101
Anterior & inferior wall	–	22
Subendocardial	–	35
Total	31	274

Includes two true posterior wall myocardial infarctions

Table II ST segment elevation

	ST segment elevation (average)
CONTROL	
Anterior wall myocardial infarction (20 cases)	2 6 mm (± 0 91) (V_1 V_3)
PERICARDITIS	
Anterior wall myocardial infarction (20 cases)	5 6 mm (± 2 25) (V_1 V_3)
CONTROL	
Inferior wall myocardial infarction (20 cases)	1 7 mm (± 1 05) (III)
PERICARDITIS	
Inferior wall myocardial infarction (9 cases)	3 6 mm (± 1 36) (III)

Two true posterior wall myocardial infarctions were not included.

Incidence of supraventricular arrhythmias (atrial flutter atrial fibrillation, paroxysmal atrial tachycardia) One patient (patient No 29) (3 2 per cent) of the group with pericarditis developed atrial fibrillation during the course of clinical pericarditis A second patient developed paroxysmal atrial tachycardia with block (patient No 9) two weeks later, at which time he had the clinical picture of a post myocardial infarction syndrome In the control group 16 patients (5 8 per cent) developed atrial arrhythmias during the first week

Congestive heart failure Significant congestive heart failure (greater than Grade I) was seen in 22 patients in the group with pericarditis (71 per cent) In the control group 141 patients (51 per cent) had a similar amount of congestive heart failure This difference is not statistically significant ($p > 0\ 80$)

Mortality rate Mortality rate refers to patients who died within 28 days of the onset of myocardial infarction Five patients (16 1 per cent) died in the pericarditis group while 33 patients (12 per cent) died in the control group Autopsy was performed on three patients in the pericarditis group

ST segment elevation The ST segment elevation seen at the onset of myocardial infarction was greater in the pericarditis group compared with controls (Table II) In those with anterior wall infarction who developed pericarditis the average ST segment elevation in the anterior precordium was 5 6 mm (± 2 25) compared to 2 6 mm (± 0 91) in the controls In those with inferior wall infarction who developed pericarditis the average ST segment elevation was 3 6 mm (± 1 36) in Lead III compared to 1 7 mm (± 1 05) in the control group

Fig 2 shows patient No 16 with evidence of acute anterior wall myocardial infarction The marked ST segment elevation had returned towards normal on day 5 at which time the pericardial rub was first heard Fig 3 shows patient No 4 with acute inferior wall myocardial infarction The pericardial rub was first heard on day 3 at which time the ST segment had returned toward normal

Discussion

Myocardial infarction is usually more extensive on the endocardial surface than on the epicardium and often does not involve the sub pericardial muscle at all[6] Even with a transmural infarction, the infarcted area is often separated from the pericardium by a layer of muscle which obtains its blood supply from the epicardial vascular network In addition in some instances, subpericardial adipose tissue prevents the infarction from extending to the pericardium[6] Pericarditis usually occurs only when the infarction extends to the epicardial surfaces[7] The presence of transmural infarction in our patients with pericarditis is consistent with these facts

Pathologically there are two types of pericarditis complicating acute myocardial infarction In the majority of instances the inflammation is localized to the area overlying the infarction but in a smaller percentage of cases generalized diffuse pericarditis may occur[8 11] The localized nature of the majority of cases of pericarditis explains why a friction rub was heard more commonly in our series in the cases with anterior

sociates[20] reported that the degree of ST segment elevation was related to the severity of experimentally produced coronary occlusion and felt that this electrocardiographic finding was a reflection of myocardial injury The correlation between the magnitude of ischemia as measured by alterations of myocardial cellular membrane potentials and the height of the epicardial ST segment has been demonstrated.[21] More recently Maroko and associates[22] have shown in the experimental animal that there is a close relationship between the extent and magnitude of early ST segment elevation in epicardial recordings after acute coronary occlusion and the later development of cellular damage as evidenced by changes in creatinine phosphokinase activity Our findings of significantly greater ST segment elevation in those patients developing pericarditis are consistent with the concept that these patients have a greater amount of myocardial injury However it is impossible to exclude the possibility that these elevations represent the earliest sign of pericarditis that exists before the clinical syndrome is appreciated

We feel that the extent of myocardial infarction is greater in those patients developing pericarditis as manifested by the increased ST segment elevation and the increased incidence of congestive heart failure In spite of these adverse findings the total mortality rate does not appear to be appreciably greater in the group with pericarditis This finding is similar to that recently reported by Thadani and colleagues [12] Earlier studies such as that of Rosenbaum and Levine[13] reported a mortality rate of 45 per cent in those with pericarditis compared to 31 per cent in the group without *pericarditis* This is very likely due to improved methods of handling complications such as major arrhythmias and congestive heart failure in modern coronary care units

The relationship between early pericarditis complicating myocardial infarction and post myocardial infarction syndrome (Dressler s syndrome) is unclear Friedberg[1] states that the two conditions often behave similarly and in cases of post infarction syndrome there is often a history of pericarditis in the first week after myocardial infarction In our series two patients (patients No 9 and 10) developed a recurrent late pericardial friction rub at day 16 and day 8 respectively In both of these cases a diagnosis of post myocardial infarction syndrome was made because of the persistence of fever pain pericardial rub and an elevated sedimentation rate These two cases in our series represent an incidence of 6 per cent of post myocardial infarction syndrome which does not seem significantly greater than that suspected in the general population of acute myocardial infarction which Dressler[23] has estimated at 3 to 4 per cent

Pericarditis within the first week of myocardial infarction rarely produces significant pericardial effusion [24] and only rare instances of hemopericardium have been reported.[25] When anticoagulation is given some reports have indicated an increased incidence of hemorrhagic pericardial effusion [26-28]

In our series 23 patients with pericarditis were anticoagulated with heparin Anticoagulation was discontinued in the two patients with post myocardial infarction syndrome as soon as this syndrome was recognized. Nine patients were not anticoagulated either because of significant hypertension or because of a history of gastrointestinal bleeding There were no instances of pericardial effusion that could be recognized clinically Autopsy performed on two patients with pericarditis who had been receiving heparin showed no evidence of hemopericardium

It is our feeling that acute pericarditis following myocardial infarction is not a contraindication for anticoagulation Patients in this category however are carefully monitored for evidence of rapidly increasing venous distention and increasing heart size Anticoagulation is discontinued if the pericardial rub persists longer than one week or if evidence of post myocardial infarction syndrome becomes obvious

Summary

The records of 31 patients with pericarditis complicating acute myocardial infarction were reviewed and compared to a control group of 274 patients with infarction but without pericarditis The cases of pericarditis all occurred within one week of myocardial infarction and were included only if a typical pericardial friction rub was heard by more than one observer

Sex distribution and age were similar in both groups There was a higher incidence of anterior wall infarction in the group with pericarditis The incidence of atrial arrhythmias was less

with the incidence being lower in those series using a more rigid definition As would be ex pected, the number of cases discovered at autop sy was greater than the number noted clinically[6]

The incidence of pericarditis might have been expected to increase with the closer and more constant observation available in a coronary care unit However, our series and the recent series by Thadani and colleagues[12] show inci dences of 10 1 per cent and 6 8 per cent, respec tively

Twenty six of 31 patients developed a pericar *dial rub between the second and fourth day* following myocardial infarction Three patients had a rub on the first day and two patients developed a rub on the fifth and seventh day This distribution is in agreement with other re ported series[12] The pericardial rub was usually transient and lasted from one to four days in 28 of our patients In one patient the rub lasted for *11 days In two cases there was late recurrence* of the rub at 8 and 16 days, and in both of these cases the clinical findings of post myocardial in farction syndrome were present

The incidence of major ventricular arrhyth mias (*ventricular tachycardia and ventricular* fibrillation) following acute myocardial infarc tion ranges between 16 and 35 per cent[15,16] The incidence of these arrhythmias was 12 per cent in our control group A 16 1 per cent incidence was noted in our group with pericarditis which is an observation in agreement with that of Thadani and colleagues[12] who found ventricu *lar arrhythmias in 23 5 per cent with pericar* ditis compared to 10 per cent in their control group In only one of our patients (patient No 31), was ventricular fibrillation coexistent with clinical pericarditis In all other instances the significant ventricular arrhythmias occurred after the pericardial rub had disappeared and was thought to be related to the increased amount of myocardial damage as manifested by the increased incidence of significant congestive failure

It has been stated *that there is an increased* incidence of atrial arrhythmias in patients with pericarditis because of the involvement of the atrium with an inflammatory process[17,18] In Soffer's series[17] of cases of idiopathic pericarditis, *13 per cent of 31* patients had transient atrial fibrillation James[18] suggested that there was an increased incidence of atrial arrhythmias during pericarditis and incriminated the anatomic proximity of the sinus node to the epicardium as a likely cause It is of interest to note, however that in his study only 6 of 38 patients with *pericarditis had recent myocardial infarction.* In addition, the group was highly selected since the 144 patients comprising the study all died of dis turbances of rhythm or conduction

Atrial flutter has been noted in less than 5 per cent and atrial fibrillation in less than 10 per cent of patients following acute myocardial in farction[16,19] In our control group these arrhyth mias were noted in 5 8 per cent of the patients while in our group with pericarditis only one pa tient (3 2 per cent) developed transient atrial fibrillation after the onset of pericarditis A sec ond patient developed paroxysmal atrial *tachycardia two weeks later during a recurrence* of pericarditis which clinically was thought to represent post myocardial infarction syndrome Thus our observations fail to show any increase in incidence of either atrial flutter or fibrillation in patients developing pericarditis within one week following myocardial infarction As was previously mentioned, the pericarditis com *plicating acute myocardial infarction* usually causes inflammation localized to the area overly ing the myocardial infarction In three cases from our group with pericarditis in whom autop sy was obtained the fibrinous reaction was localized to the ventricles in the area of the in farction The atria and the area overlying the sinus node were intact It is this anatomic obser vation that explains the lack of an increased in cidence of atrial arrhythmias in our cases with pericarditis It also explains why a significant *difference exists between series of generalized* pericarditis and post infarction pericarditis

The relationship between pericarditis and the extent of myocardial damage remains an impor tant unanswered question Thadani and col leagues[12] felt that the patients did have a greater amount of myocardial damage as manifested by the increased incidence of major arrhythmias and increased radiographic evidence of conges tive heart failure We attempted to evaluate the extent of myocardial injury by measuring the magnitude of ST segment elevation at the time of onset of myocardial infarction In every in stance these determinations were made before the onset of clinical *pericarditis Wegria* and as

Current concepts of therapy with digitalis glycosides Part I

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The digitalis glycosides have been keystone compounds in the treatment of cardiac disorders since Withering s studies in 1785 These compounds are now the fourth most commonly prescribed medication in this country

We have learned much about the pharmacology of these agents and their clinical use since 1966 when this subject was last reviewed in the AMERICAN HEART JOURNAL[1] Basic scientists have provided evidence that the inotropic effect of the digitalis glycosides is probably mediated through their effects on membrane systems that control the interrelated movements of sodium potassium and calcium But perhaps of greater importance to the clinician has been the further use of radiolabelled compounds to study the clinical pharmacology of the glycosides and the development of sensitive and accurate assays for glycoside levels in the blood These new techniques have opened up a whole new quantitative aspect to the study of the digitalis glycosides It is the purpose of this communication to survey current concepts in the use of digitalis and to review how some of the information derived from recent research has enhanced our understanding of the use of digitalis glycosides in clinical cardiology

Assay of digitalis glycosides

A large number of methods for the assay of digitalis glycosides have been devised and are detailed in recent reviews[2,3] Until 1969 most studies relating to the pharmacology of digitalis glycosides in man depended upon the use of radiolabelled tracers A practical radioimmunoassay was described in 1969 Since this technique employs a displacement of radioactive glycoside from an antibody other radioactive compounds administered for diagnostic or therapeutic purposes may interfere with this assay method

Other useful assay systems are based upon the fact that all mammalian cells have a membrane bound Na^+ K^+ stimulated adenosinetriphosphatase (ATPase) that can be inhibited by digitalis glycosides Employing this principle the inhibitory effect of digitalis upon the uptake of ^{86}Rb by erythrocytes was used to assay digitalis concentration In another assay system radiolabelled ouabain is bound to a purified membrane Na^+ K^+ ATPase The ouabain is displaced in a quantitative fashion by unknown glycoside This test has been applied to the measurement of serum digoxin digitoxin and digitalis leaf Those methods that depend upon inhibition of Na^+ K^+ ATPase by cardiac glycosides measure biological activity While radioimmunoassay measures the parent compound most strongly there may be some reactivity with breakdown products (total immunoreactivity) Thus when the breakdown products have a high level of biological activity as may occur with digitoxin the membrane Na^+ K^+ ATPase tests should theoretically provide a better therapeutic indicator of digitalis level This supposition remains to be verified by actual testing On the other hand the serum used for the membrane Na^+ K^+ ATPase tests must be extracted whereas with radioimmunoassay direct exposure of the test medium to serum is all that is necessary

The blood levels of digitalis glycosides as

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than in controls while the incidence of ventricular arrhythmias, significant congestive heart failure, and death was slightly greater in those with pericarditis

Maximum ST segment elevation on the day of admission in the group with pericarditis was compared with a control group In those with an terior wall infarction and pericarditis, the average ST segment elevation in the anterior precordium was 5 6 mm compared to 2 6 mm in the controls In those with inferior wall infarction and pericarditis the average ST segment elevation was 3 6 mm in Lead III compared to 1 7 mm in a control group

It is concluded that patients who develop pericarditis within one week of acute myocardial infarction do not have an increased incidence of atrial arrhythmias The incidence of ventricular arrhythmias, significant congestive heart failure, and death are slightly greater and may be due to more extensive myocardial infarction The higher initial ST segment elevation in patients with pericarditis may indicate a greater amount of injury or may be a sign of pericardial involvement that is seen before clinical pericarditis is present

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is influenced by the action of digitalis on the peripheral vasculature and by the presence or absence of depressed ventricular function or cardiac failure prior to administration of the drug. These differences can be brought out in borderline cases by stressing the heart with an increased hemodynamic load.

In normal subjects digitalis will increase venous tone and cause arterial constriction tending to increase peripheral vascular resistance. As a result of these cardiac and peripheral effects cardiac output will remain unchanged or decline in normal man. The patient with heart disease, normal resting hemodynamics and no evidence of congestive heart failure may have an inadequate cardiac output response to exercise. This can be partially corrected by digitalis. When congestive heart failure is present this condition is usually associated with increased peripheral arterial and venous resistances. In this case digitalis will directly augment cardiac output and reflexly diminish vascular tone. In a variety of animal studies cardiac glycosides have been shown to cause splanchnic arteriolar constriction. A word of caution is suggested because a possible relation between digitalis and mesenteric vascular ischemia has been observed in man.[7] In the vast majority of instances patients with fatal ischemic bowel disease have been on digitalis.

There are few studies of the effect of digitalis on the pulmonary vasculature. Acute administration of acetyl strophanthidin to a group of patients having a variety of cardiac diseases resulted in no direct action on the pulmonary vessels.[8] Decreases in pulmonary blood volume and pulmonary artery diastolic pressure observed in some patients were largely secondary to the inotropic effect of digitalis on the left ventricle. Changes in pulmonary vascular resistance were inconsistent.

Clinical pharmacology of digitalis glycosides serum levels

The availability of accurate determinations of digitalis blood levels has led to a better understanding of absorption, metabolism and excretion of these agents.[9] In this regard the pharmacokinetics of digoxin have been more completely studied than any other glycoside.

The clinical utility of a particular serum level of a cardiac glycoside presupposes that the blood specimen was drawn at a time when serum and tissue digitalis have reached a stable equilibrium. In the case of digoxin this would be at least six hours after the previously administered dose. We assume that the serum glycoside level is directly related to the myocardial level. Information on this question appears to support this assumption with regard to digoxin. However few data are available with regard to the other clinically useful cardiac glycosides. Serum and presumably myocardial levels of digitalis glycosides are directly related to toxic manifestations. However a significant overlap between toxic and therapeutic serum levels has been noted in various studies so that a single serum cardiac glycoside level must be interpreted within the total clinical picture.

A further difficulty with serum glycoside measurement relates to the radioimmunoassay techniques and the measurement of serum digitoxin. It is not entirely clear whether this assay technique measures metabolic derivatives of digitoxin with cardiac glycoside activity or whether the glycoside measured by the immune technique bears a constant ratio to cardioactive glycoside metabolites. This latter consideration is of no significance with regard to digitalis preparations which do not undergo significant metabolism in man.

Several of the cardiac glycosides are extensively bound to serum albumin. It is the unbound free glycoside which is pharmacologically active. Current assay techniques measure the total serum concentration. While in most clinical situations the free drug concentration bears a fairly constant portion of the total, alterations in serum albumin or other agents that bind to serum albumin may alter the level of the unbound glycoside.

About 85 per cent of tritiated digoxin is absorbed when administered orally in alcoholic solution to normal human subjects. After intake of digoxin tablets approximately 75 per cent is absorbed. There appears to be a large variation of bioavailability of various brands of digoxin tablets and even within different lots of some manufacturers' products.[10]

The primary site for absorption of digoxin is in the small bowel, although a small amount may traverse the gastric mucosa. Thus, when the small bowel is diseased, causing malabsorption syndromes, digoxin uptake is decreased and er

measured by these various techniques appear to be similar, but the methods have not been directly compared using large numbers of the same samples

The radioimmunoassay test can be performed upon larger groups of samples more rapidly and with greater ease than can the other tests For this reason it is the most widely used method for digitalis assay at this time

Pharmacologic effects of digitalis on the myocardium

Digitalis affects the cardiovascular system through two important mechanisms a positive inotropic effect and an alteration of the elec trophysiology of the heart[4] The inotropic effect appears to be similar in direction throughout the myocardium The effects on transmembrane po tential and conduction vary considerably in different portions of the heart Considerable knowledge in each of these two spheres has been acquired in recent years but the exact relation between the effects of digitalis on cardiac elec trophysiology and on inotropism await further biophysical and biochemical investigation

For a long time there was considerable dispute about whether digitalis had a direct effect upon the strength of contraction, or whether its efficacy was mainly mediated by controlling the ventricular response to atrial fibrillation Numerous studies now have documented that digitalis increases the contractile state of the myocardium (both the force and the velocity with which the muscle contracts) and that this effect is a function of the concentration of the agent

Digitalis also has many different effects on excitability, automaticity conduction velocity, and refractoriness of myocardial cells and the conduction system Beside the direct effect upon heart muscle digitalis has vagotonic (cholinergic) action on the conduction system particularly at the atrioventricular node The specific effects their degree, and even direction depend on the type of tissue in the heart being studied The direct effects of digitalis and its vagal effect may reinforce or oppose each other either may become clinically more important de pending on the region of the heart digitalis level, and pre existing autonomic tone Those effects that are most important clinically are increasing the automaticity of pacemaker sites outside the sinoatrial node, and prolonging the rate of con duction and the refractory period particularly through the atrioventricular junction Digitalis can revert supraventricular tachyarrhythmias to normal sinus rhythm by its direct effect on decreasing atrial conduction velocity and by shortening the atrial refractory period by its in direct vagal effect

Digitalis glycosides do not appear to have a direct effect on contractile protein interaction Instead current information suggests that digitalis compounds are specific in binding to Na^+, K^+ activated membrane ATPase of the heart as well as of other tissues[5] Digitalis binds to the enzyme changing its conformation and leading to an inhibition of its transport function Digitalis does not compete directly with Na^+ or K^+ for binding to Na^+, K^+ activated membrane ATPase but is bound to an allosteric site Experi mentally, no inotropism has been elicited by digitalis unless some paralysis of the enzyme has also been demonstrated Therapeutic doses of digitalis augment Ca^{++} influx in the cell, and Ca^{++} plays the central role in excitation contrac tion coupling process in muscle This influx of Ca^{++} into the cell and inhibition of the Na^+, K^+ membrane pump apparently are related but the intricacies of the relationship are subjects of cur rent study

The toxic effect of digitalis may be related to an exaggeration of the inhibition of Na^+, K^+ membrane ATPase allowing larger amounts of potassium to leak out of the cell and making it more susceptible to electrical instability

Effects of digitalis glycosides on integrated cardiovascular function

The effects of digitalis upon the normal and failing heart have been reviewed extensively[6] In general, the effects upon the function of the myocardium (heart as a muscle) ventricular function (heart as pump) and the peripheral vasculature may be considered separately in nor mal subjects those with hypertrophy but not cir culatory failure and those with overt circulatory failure

In all three hemodynamic states digitalis will cause an increase in the contractility of the myocardium by its direct inotropic action The ventricular function curve (stroke work versus end diastolic pressure) will also be improved However the effect of digitalis upon cardiac out put per se can vary according to the clinical state

achieve equilibrium with a daily dose because of the longer half life the daily digoxin dose must be diminished When these facts about digoxin metabolism have been emphasized in prescribing the drug the incidence of digoxin toxicity has been shown to be reduced.[19]

Studies of digoxin pharmacokinetics in infants and children indicate that tissue distribution of digoxin half life and excretion are similar to those seen in adults[20] Recommended doses of digoxin for children are two to three times greater than those for adults on a milligram per kilogram basis and serum digoxin levels are sig nificantly higher in children given therapeutic doses of digoxin[21] Children tolerate significantly higher serum concentrations than adults on usual maintenance digoxin therapy

Digitoxin is more completely absorbed from the gastrointestinal tract than digoxin ap proaching 100 per cent Studies in dogs indicate that digitoxin is rapidly absorbed into the portal venous blood[22] Peak concentrations are reached within 15 minutes Hepatic metabolism and bili ary excretion of digitoxin delay its appearance in systemic veins so that peak systemic concentra tions are not achieved until 45 minutes after oral administration Digitoxin is almost completely bound to serum albumin This large bound to free ratio probably explains the fact that serum digitoxin levels are about 20 times serum digoxin levels for a comparable therapeutic effect Fif teen to 20 per cent of total body stores of digitox in are excreted per day yielding a serum half time of approximately four to six days[9] Because of the prolonged serum half life patients given maintenance doses of digitoxin require about one month (four to five half lives) to reach kinetic equilibrium and stable total body stores Therefore loading doses are almost always nec essary with digitoxin Unlike digoxin digitoxin undergoes metabolism primarily by the liver and its metabolic products appear to have at least some pharmacologic effects[23] Twenty six per cent of total body digitoxin undergoes en terohepatic circulation Most of the digitoxin that is excreted in the bile is reabsorbed in the gastrointestinal tract and only 2 per cent is ex creted in the stool daily This intestinal phase of the enterohepatic circulation has been used to remove digitoxin from the body by the use of bile sequestering agents Digitoxin is also excreted by the kidneys but to a lesser degree than digoxin Its metabolic products are also excreted by the kidneys so that of the digitoxin leaving the body about 85 per cent appears in the urine primarily as inactive metabolites However because of its hepatic metabolism impaired renal function only minimally affects the serum level and half life of the active glycosides

Unlike the case with digoxin the variations in total body digitoxin in different patients on a given chronically administered dose are narrow Drugs that bind to serum albumin may displace digitoxin in vitro from its binding sites This has not been proved to be of importance in vivo Cer tain medications that alter liver metabolism af fect digitoxin blood levels These include inducers of hepatic microsomal enzymes such as pheno barbital diphenylhydantoin and phenylbuta zone all of which may lower digitoxin blood levels[24] While renal insufficiency does not pro long serum half life of digitoxin significantly it seems logical that impaired hepatic function would. However we are not aware of careful studies that document this supposition

Some clinicians advocate the routine use of digitoxin because of the relatively slow excretion of the drug resulting in only minor fluctuations in serum levels over a 24 hour period when com pared to digoxin[25] However the prolonged half life of digitoxin has the negative feature of resulting in longer duration of toxicity should overdosage occur

Ouabain is poorly and erratically absorbed by the oral route and should be administered in travenously Plasma kinetic studies performed in man have indicated a half life of 21 hours[26] The kidneys are the primary route of excretion with 50 to 60 per cent of an intravenous dose of H^3 ouabain found in the urine over a 24 hour period Renal insufficiency has been shown to promote higher serum levels of ouabain and prolong the half life of this agent A positive inotropic effect is noted within 20 minutes after intravenous ad ministration of ouabain Ouabain may undergo biotransformation in the body or may be ex creted in significant amounts by a nonrenal route Several studies have indicated that the onset of action of intravenous ouabain is not sig nificantly different from that of deslanoside and only slightly faster than that of digoxin

The relation of digitalis glycosides to systolic time intervals

The measurement of systolic time intervals has become a popular noninvasive method for

ratic[11] Patients with these conditions may have to be followed more carefully with serial serum digoxin determinations Pancreatic insufficiency does not appear to alter digoxin absorption

Digoxin administration by the intramuscular route results in a slower and more erratic absorption pattern than the oral or intravenous route and is also attended in some patients by a considerable amount of pain

After oral administration to fasting subjects digoxin is detected in the serum in 15 minutes and peak serum levels are achieved in approximately one to two hours During this period the glycoside is being distributed through the body tissues so that after two hours its decay phase begins The serum level decreases with a half time averaging 36 hours Digoxin losses from the body are directly related to total body digoxin Thus approximately 33 per cent of total body digoxin is excreted per day and must be replaced to maintain constant levels These figures pertain to normal males

Serial plasma and myocardial digoxin assays obtained in dogs indicate that the hemodynamic effects of digoxin lag behind the myocardial concentration suggesting that total myocardial digoxin is not the only determinant of the rate of onset and strength of the inotropic action of digoxin[12] Also of interest is the observation that myocardial concentration of digoxin is not uniform throughout the heart the difference in distribution possibly being related to variations in blood flow throughout the myocardium

Approximately 25 per cent of the circulating digoxin is bound to albumin and the remainder exists in the unbound state The fact that a large proportion is not bound to a serum protein may be responsible for its relatively rapid excretion via the kidneys and its passage through the placental membranes to the fetus

The concentration of digoxin differs in various tissues with the greatest concentration found in the kidney[9] These distribution patterns do not appear to be affected by the changes in the total body digoxin or various disease states The heart has about half the concentration of the kidney and the ratio of heart to serum concentrations ranges from 20 1 to 50 1 with a mean near 30 1 Although skeletal muscle has about one fifth the concentration of digoxin found in the heart, the total amount of digoxin bound to skeletal muscle is quite high and might serve as a reservoir for shifts to other tissues

In experimental animals hyperkalemia while not affecting serum digoxin levels lowers myocardial binding of digoxin for any given serum level and decreases the inotropic response proportionately[13] However, once digoxin is bound to the myocardium hyperkalemia will not lower myocardial digoxin levels[14] Hypokalemia has the opposite effects on myocardial digoxin concentrations and upon its inotropic effect[15]

Digoxin is not metabolized in the body but is mainly cleared from the serum unchanged by the kidney A small enterohepatic circulation has also been demonstrated Its clearance is proportional to the creatinine clearance, and thus the half time for serum digoxin is prolonged in relation to decreased renal function In anephric patients approximately 5 per cent of digoxin is excreted into the gastrointestinal tract per day

The serum level of serum digoxin for any dose appears to relate to lean body mass As patients age and their lean body mass and creatinine clearance decline the digoxin dose should be reduced accordingly[16]

Hypothyroid patients are more sensitive to the therapeutic effects of digitalis the reverse is true of hyperthyroid individuals Studies with tritiated digoxin given human subjects who were euthyroid hyperthyroid or hypothyroid indicate that serum digoxin levels are inversely related to thyroid function[17] However the serum half life of digoxin is not altered by the thyroid status in humans Furthermore animal studies indicate that the tissue distribution of digoxin is unaffected by alterations in thyroid function

There are no alterations in serum levels half life or excretion rates of digoxin between patients with and without congestive heart failure Absorption of oral digoxin in patients with congestive failure has not undergone extensive investigation

It has been demonstrated that with administration of a constant daily dose of digoxin stable serum levels are achieved four to five half lives after initiation of therapy[18] Thus patients with normal renal function develop stable blood levels in six to eight days (four to five half lives) If the need for a therapeutic level of digoxin is not urgent loading doses are not required The absolute serum level of digoxin that will be achieved after four to five half lives will depend upon the amount of digoxin administered versus the amount of excreted daily in the urine Thus with renal failure although it will take longer to

Annotations

Of controls

A most important aspect of research, and especially clinical research is the *controls* However what constitutes controls is poorly or not even understood in some instances Controls are particularly important in all therapeutics and certainly in the therapeutics in cardiology Reliable evaluation of a new drug or operative procedure is most difficult to obtain Comparing data obtained from mice rats and dogs with data from sick people can be misleading and even hazardous. Such experimental animals do not develop many diseases that men do This is well exemplified by studies of coronary artery disease These experimental animals do not have ischemic heart disease as a spontaneous health problem yet observations on them are applied to coronary heart disease in man. There can be no truly significant controls for coronary arteriosclerosis when studying experimental animals

Too often normal people serve as a control for people with a given disease But other people with other diseases must be included among the controls Drugs for example act quite differently in patients with various diseases Because a substance is increased in the blood of a patient with pneumococcic pneumonia and not in normal people it does not necessarily mean that this elevation is characteristic only for pneumococcic pneumonia The substance might also be increased in nephrosis pyelonephritis streptococcic pharyngitis *or some other disease Because a new operation* relieves the pain of a certain group of patients it does not necessarily mean the operation is specific for the type of disease common to these *patients Double blind studies sham* operations and other rigorous control studies are needed before drugs operations or procedures are introduced for general use Investigations of the influence of these therapeutic measures on the course of the disease and even on life expectancy are needed for adequate and final evaluation

The use of anesthetics[1] other drugs and procedures as well as unfavorable reactions complications and many other factors could so influence investigative results that proper control studies become even more significant and difficult to provide

Readers should be careful always to evaluate the control studies extremely meticulously and critically when reviewing and reading publications especially those few that introduce new ideas and concepts

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Temperature chart analysis in the diagnosis of deep vein thrombosis

The introduction of radioisotope tests has drawn attention to the frequency with which thrombi occur in the leg veins following surgery the incidence of 30 per cent has been commonly reported[1] The validity of this technique has been well shown when compared with phlebography which remains the definitive diagnostic technique[1] Patients who have recently suffered a myocardial infarction have a similarly high incidence of deep vein thrombosis(D V T)[2,3]

Careful clinical examination will detect up to 50 per cent of these thrombi[4] Fever has long been regarded as a sign of D V T but its importance is often masked by the coexistence of other causes of fever We believe that we *could* recognize a pattern of fever which was commonly associated with D V T[5] The features of this fever were (1) temperature between 37 4 C and 38 0 C., (2) duration of not less than 2 days (3) no fever for 24 hours before the suspected onset of the D V T and (4) first and second postoperative days excluded.

These criteria were applied retrospectively (55 patients) and prospectively (89 patients) All patients had radioactive fibrinogen studies performed for the detection of calf vein thrombosis

The results showed that half the thrombi (20/40 could be detected by analysis of the temperature charts alone In 6 2 per cent (9/144) a false positive diagnosis was made Detection of half the patients who have thrombi is not particularly satisfactory unless reasons for failure can be *found.* Further analysis showed that the thrombi which were not detected by this method were of shorter duration than those with this fever pattern, and only one undetected thrombus extended to involve the axial venous system It follows from this that an afebrile patient is highly unlikely

evaluating some features of cardiac function When the aortic diastolic pressure does not change alterations in the pre ejection period correlate relatively well with the changes in contractile state of the heart When the ventricular end diastolic pressure, the aortic pressure, *heart rate, and stroke volume remain constant,* changes in the ejection time also correlate with contractility

Systolic time intervals have been employed to measure the time of onset and duration of action of the various digitalis glycosides in normal subjects and results correlate well with pharmacologic studies employing direct measurements of blood levels Systolic time intervals have also been used to measure the effect of administration of digitalis to patients with congestive heart failure In general these agents shorten both pre ejection period and ejection time, implying a higher dP/dt and mean rate of left ventricular ejection [27] However because of a large variability between patients and the many factors *mentioned* above that *may alter systolic* time intervals independent of contractility these simple measurements have not gained wide acceptance as a tool for following the course of patients *being treated with digitalis*

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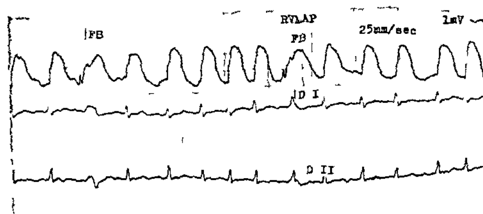


Fig 2 Simultaneous recording of right ventricular monophasic action potential (RVMAP) and Leads D_I and D_{II} The third and the ninth complexes are ventricular fusion beats For discussion see text Paper speed is 25 mm per second

mature beats arising from the multiple foci or in atrial fibrillation with aberrant supraventricular beats Certain cases of minimal electrocardiographic deviation heretofore considered nonspecific and unrelated to premature activation may in fact be the result of ventricular premature beats.[1,2,6]

In Fig 2 two ventricular fusion beats are presented There is a simultaneous recording of right ventricular monophasic action potential with Leads D_I and D_{II} of the standard electrocardiogram The third and the ninth complexes have the same shape with a slow slope of phase O and a large base The corresponding QRS complex s on the standard electrocardiogram are wide and different in shape with different coupling intervals (680 msec for the first and 640 msec for the second) In this situation a parasystole is to be taken into account The underlying rhythm is an atrial fibrillation

In these two instances presented in Figs 1 and 2 the recording of MAP is useful for the diagnosis and the understanding of atrial and ventricular fusion beast

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Small doses of subcutaneous heparin in preventing postoperative deep venous thrombosis

Soon after heparin was isolated, it was found to be of value in preventing thromboembolism However the difficulties of its administration and control, and the risk of bleeding prevented its widespread use in surgical patients

The observation that patients with shortened Lea White coagulation times of 2½ to 4 minutes (normal 5 to 10 minutes) submitted to operation were at risk of venous thrombosis[1] led Sharnoff to sugg st the minimum of anticoagulation to maintain normal coagulation as a means of preventing thrombosis without excessive bleeding[2,3] Ten

to develop a thrombosis which could carry a high risk of serious pulmonary embolus However a febrile patient may harbor a thrombus which may not be detected either by clin ical examination or study of the temperature chart

As efficient prophylactic techniques are developed the cost benefit of the routine use of diagnostic studies becomes less Screening procedures which indicate the patients at high risk then become important in planning the optimum use of these resources This study suggests that temperature chart analysis defines a group of patients at high risk for harboring a D V T and allows the concentration of diag nostic studies to this group

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Fusion beats demonstrated by MAP suction electrode technique

The monophasic action potential (MAP) recorded using an electrode technique[3 5] may provide additional information concerning the ventricular and atrial fusion beats The amplification of electrical events during atrial and ventricu lar repolarization obtained with this technique allows a bet ter insight into electrophysiological phenomena

Fusion beats have been called combination or summa tion beats The appearance of an intermediate or mixed complex takes place if two impulses from different foci ar rive more or less simultaneously in the heart each impulse activating a part of the chamber involved [2 7]

Atrial fusion beats may occur when the ectopic beat ap pears very late in the cycle of basic rhythm and when the sinus node fires the impulse just before the ectopic impulse reaches it Atrial fusion beats are usually due to a sinus im pulse fusing with a retrograde impulse of an A V junctional or ventricular beat One rarely finds fusion of the sinus im pulse with an atrial premature beat [1 7]

In Fig 1 an atrial fusion beat is shown It represents a si multaneous recording of right atrium monophasic action po tential with Leads V_3 and D_I of the standard electrocar diogram The third complex is a premature atrial beat with a coupling interval of 400 msec The fifth complex is another atrial premature beat with a coupling interval of 460 msec It is conducted to the ventricles producing a large QRS com plex and does not disturb the appearance of sinusal complex at the same atrial cycle length (640 msec) which is blocked On the MAP recording it is possible to observe the fusion be tween the two action potentials which cannot be seen on the standard electrocardiogram The two atrial premature beats may be considered as a parasystole The MAP duration measured at the base line is 280 msec except the complex preceding the fusion beat which lasts 320 msec We have no explanation for this lengthening of MAP duration before the fusion beat.

Ventricular fusion beats result from the fusion of a supra ventricular impulse with a ventricular premature beat These beats may be confused in some instances with pre-

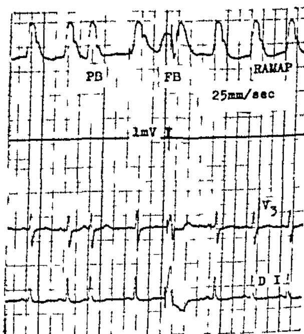


Fig 1 Simultaneous recording of right atrial monophasic ac tion potential (RAMAP) and Leads V_3 and D_I The fifth com plex is a fusion beat For discussion see text Paper speed is *25 mm per second*

has been established that if small dose subcutaneous heparin is to be effective it must be administered before operation and must be continued for as long as possible in the postoperative period Although most of the thrombi oc cur at the time of operation or soon after 10 per cent will oc cur after the fifth postoperative day Despite the difficulties and the work ahead this may be the beginning of a period during which the incidence of postoperative deep venous thrombosis and pulmonary embolism will be diminished.

Most of the advances in the diagnosis and prevention of venous thrombosis in recent years have been made by surgeons and it is natural that most studies were conducted in surgical patients The problem of thromboembolism is just as great in medical patients—for example 13 per cent of cardiac patients who die die from pulmonary embolism [30] Therefore it is hoped that studies in these patients might be even more rewarding

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thousand international units of sodium heparin were administered subcutaneously about 10 hours before operation and then 2 500 units every six hours until the patient was fully active or discharged There had been one confirmed death from thromboembolism in 750 patients treated with the above regimen as compared to one in 90 cases among 18 729 without the prophylactic administration of heparin There were only two instances where excessive bleeding at operation was attributed to heparin this being traced to inadvertent incorrect administration of the anticoagulant The main criticisms of Sharnoff's work has been that it was not a controlled trial and that somewhat less than 40 per cent of the patients who died in each group had necropsies [4]

The introduction of the ^{125}I Fibrinogen test[5] by means of which a thrombus forming in a patient can be detected with precision has shown that the incidence of deep venous thrombosis is high not only in general surgical patients (30 per cent[6,7]) but also in gynecological (18 per cent[8]) orthopedic (50 per cent[9]) and urological patients (28 per cent[10,11]) In all these patients practically all thrombi had commenced in the calf and particularly in the soleal veins[12] where stasis occurs [13] Fifty per cent of the thrombi commenced during the operation [14]

We know that the majority of thrombi detected by the ^{125}I Fibrinogen test are harmless because they do not produce emboli they either remain localized in the calf or lyse spontaneously [15] However 20 per cent extend proximally into and above the popliteal vein and are then liable to break off and become emboli It has been estimated that when they extend into the pelvic veins the incidence of pulmonary embolism becomes approximately 50 per cent [16]

The fact that most thrombi start in the calf at the time of operation or soon after means that the factors responsible for intravascular coagulation produce their maximum effect there at this particular time It has been demonstrated that immediately after injury contact factors are found circulating in the blood in an activated form [17] The production of thrombi has been shown to depend on the presence of such activated factors in an area of stasis [17] However thrombosis is not produced by stasis alone or by activated factors alone but by a combination of the two [17]

The theoretical basis for the use of small doses of subcutaneous heparin to prevent deep venous thrombosis stems from the identification of a potent naturally occurring inhibitor to activated factor X in human plasma [18] and the observation that the activity of this inhibitor (antithrombin III) is enhanced by heparin [19] Activated factor X occupies a key position in the intrinsic and extrinsic coagulation mechanisms If heparin is administered before the tissue trauma activates factor X, then low doses of heparin are quite adequate to prevent thrombosis The same doses of heparin given after tissue trauma are ineffective as at this stage larger doses are required to inhibit the thrombin fibrinogen reaction [19]

It has also been demonstrated that bacterial endotoxin activates factor XI to XIa producing a hypercoagulable state and thrombosis in areas of venous stasis This can be prevented experimentally by as little as 10 units of heparin per kilogram of body weight injected intravenously a dose insufficient to prolong the clotting time [20] In a series of 330 general surgical patients screened with the ^{125}I Fibrinogen test the incidence of deep venous thrombosis was 20 per cent in patients without infection and 55 per cent in patients who developed postoperative infection The increased incidence in the latter group was due to a large number of thrombi occurring between the third and eighth postoperative days [21]

Kakkar and his colleagues[22,23] and Williams[24] produced evidence that small doses of subcutaneous heparin reduce the incidence of postoperative venous thrombosis as detected by the ^{125}I Fibrinogen test Gordon Smith and his colleagues[25] in a recent controlled trial of two regimens of subcutaneous heparin one administered for 24 hours and the other for 5 days demonstrated that the incidence was reduced from 42 per cent in the control group to 13 5 per cent and 8 3 per cent in the test groups respectively These trials involved a relatively small number of patients and conclusions on the efficacy of small dose subcutaneous heparin in preventing postoperative pulmonary embolism could not be made

The latest trial has involved 244 patients over the age of 40 undergoing elective major general surgery or thoracic operations [26] The patients were randomly allocated to a control and test group Subcutaneous sodium heparin (5 000 international units in 0.2 ml) was administered to the patients in the test group two hours before operation and then twelve hourly for seven days All the patients were screened with the ^{125}I Fibrinogen test During the period of heparin administration the incidence of deep venous thrombosis in the control group was 23 per cent and in the test group 0 8 per cent. There was no difference in blood loss or hematoma formation in the two groups The thrombi were first detected in the calf in all patients who developed venous thrombosis. There was a subsequent proximal spread of the thrombi in nine patients in the control group

The results of this trial demonstrated that small dose subcutaneous heparin could safely prevent not only the early postoperative thrombi detected by the ^{125}I Fibrinogen test but also their dangerous proximal extensions which are often responsible for pulmonary emboli

In some previous studies[22,23] calcium heparin has been administered Using a quantitative and sensitive assay[2] no difference in the heparin blood levels of the two types of heparin have been detected following a subcutaneous injection of 5 000 international units in volunteers.[28] It has been suggested that the calcium salt causes less local bleeding than the sodium salt [29] However local hematoma following the injection of 5 000 international units of sodium heparin was not a problem in any of the other trials [25,26]

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For the first time rational accounts are available of how venous stasis and the hypercoagulable state can result in thrombosis and how thrombosis can safely be prevented. It

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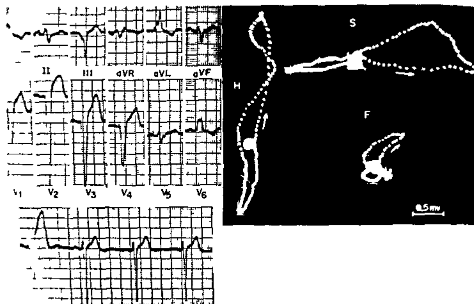


Fig 2 In the same patient the development of LBBB suppresses the electrocardiographic and vectorcardiographic signs of inferior myocardial infarction The initial forces of the QRS loop have been shifted inferiorly projecting an r wave in Lead aV_F

2 Horan L G Flowers N C and Johnson J C Significance of the diagnostic Q wave of myocardial infarction Circulation 43 428 1971

Reply

To the Editor

A review of the articles by Horan and associates to which Dr Flowers referred, reveals that the conclusions drawn from the study are well founded, although it would have been desirable if stricter criteria for abnormal Q waves (Q wave duration of 0 04 second plus a depth equal to 25 per cent or more of the following R wave not valid for Leads III aV_L and V_1 or a QS pattern) were taken into consideration in the analysis of their cases Otherwise we believe that the results obtained with regard to the Q waves in inferior leads are not significantly different from those reported in our study Fig 5 in the article by Horan and associates (Chest 58 219 1970) shows a frequent localization of the myocardial lesions to the inferior regions in patients with LBBB even though Q waves in the inferior leads were detected in only eight of those cases almost confirming our results which indicate that in most of the patients the development of LBBB suppresses the electrocardiographic signs of inferior myocardial necrosis Therefore it could be stated that the presence of abnormal Q waves in the inferior leads is diagnostic of infarction even in the presence of complete LBBB but their absence does not necessarily exclude this diagnosis In other words abnormal Q waves in Leads II III and aV_F in patients with LBBB have a high specificity when present

Since our article appeared, we have seen a new case see Figs 1 and 2

In patients with LBBB and anterior Q waves our results differ from those obtained by Dr Flowers and her group This difference may be due to (1) the nature of the two studies since ours dealt exclusively with intermittent LBBB and (2) the small number of cases in our series As Dr Flowers pointed out a larger series might disclose abnormal anterior Q waves in the absence of myocardial infarction

LBBB still remains a puzzling problem Further comparative serial studies in a large number of cases of myocardial infarction with normal intraventricular conduction with LBBB with and without myocardial infarction as well as in normal subjects would shed more light on this problem

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Letters to the Editor

Effects of left bundle branch block on ECG patterns

To the Editor

The article entitled Intermittent left bundle branch block A study of the effects of left bundle branch block on the electrocardiographic patterns of myocardial infarction and ischemia by Luy Bahl and Massie which appeared in the March 1973 issue of the JOURNAL, was of particular interest to me and my co workers because its conclusions were somewhat different from those arrived at when electrocardiographic anatomic correlation was attempted in 72 patients with complete and 44 with incomplete left bundle branch block (LBBB) In the latter studies[1,2] in which the detailed postmortem dissections were done according to protocol by the same individuals diagnostic Q waves were frequently seen in those without evidence of myocardial infarction as well as those with it The only exception to this occurred in the eight patients with diagnostic Q waves in Leads II III or aV_F all of whom had evidence of infarction in the presence of LBBB In four of the six with incomplete LBBB and diagnostic Q waves in Leads II III and aV_F there was evidence of scarring The presence of diagnostic Q waves in Leads V_1 through V_4 or in Leads I aV_L V_5 or V_6 was far less helpful in distinguishing those with anatomically documented infarction from those without it When the presence of infarction was not known by other independent criteria the finding of diagnostic Q waves anteriorly or laterally was not diagnostic of infarction it occurred in 24 of 68 patients with infarction and in 19 of 48 without The finding of Q waves inferiorly however suggested concomitant myocardial infarction with no false positives in the complete LBBB group

Our data cause us to doubt the assumption that there is sufficient predictability and uniformity of ventricular activation in the presence of LBBB to validate criteria for the diagnosis of infarction based on single vectorcardiographic or electrocardiographic reports When the series studied is sufficiently large and includes many subjects without infarction, abnormal Q waves are likely to be found in patients without myocardial infarction but with LBBB These contentions should not be interpreted as suggesting that we abandon the good clinical dicta about observing *change* Certainly the physician should utilize other independent data and presume infarction if a new block appears if the block suddenly changes form or if the ST segment drastically shifts magnitude but should be wary of extrapolations beyond these

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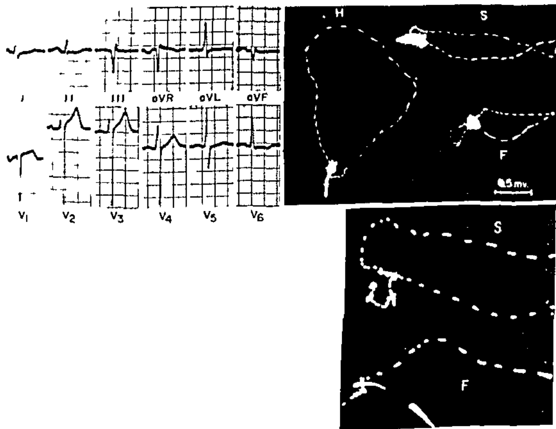


Fig 1 Electrocardiogram and vectorcardiogram of a 58 year old man with a documented old myocardial infarction *Note* pathologic Q waves in Leads III and aV_F The vectorcardiogram shows the characteristic features of inferior wall myocardial infarction well seen in the frontal and sagittal plane

American Heart Journal

March, 1974 Volume 87 Number 3

Editorial

The cause effect relationship between recent coronary artery occlusion and acute myocardial infarction

Irving Chapman M D*
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Previously it was generally accepted that an acute myocardial infarction was caused by a recent coronary artery occlusion The diagnostic terms of occlusion and infarction were used interchangeably In 1956 Branwood and Montgomery[1] challenged this assumption and suggested that a coronary artery thrombosis may be a consequence of the infarct Their viewpoint was supported by other investigators[2 7] These diametrically opposed opinions are uncomfortably confusing and unless this difference is resolved, there will be uncertainty as to the approach *in the investigation of myocardial* infarction

The evidence most frequently submitted by those who doubt the cause effect relationship between occlusion and infarction is the low association of the two at autopsy[1 6] Additional supportive observations are (1) that when a coronary artery occlusion and myocardial infarction are associated they are not coeval[1 5] (2) that extensive anastomosis between sclerotic coronary arteries[5] will usually prevent an infarct when an extramural branch of a coronary artery is occluded, (3) that the incidence of coronary artery occlusion at autopsy increases in direct proportion to the length of survival of the patient with myocardial ischemia[2] and (4) when ^{125}I labelled fibrinogen is administered intravenously after the clinical inception of an infarct radioactivity is found throughout the entire thrombus[7]

Each of these articles of evidence will be discussed in sequence

In 1968 I[15] reported an autopsy study of 303 *acute transmural infarcts in 292 hearts* A recent coronary artery thrombosis was associated with 278 infarcts (91 4 per cent) Since then I have examined an additional 125 instances of acute transmural infarcts in 123 hearts and a recent occlusion was associated with 115 (92 per cent) In all but two instances the occlusion was in an artery which subtended the infarct

My findings were in remarkable agreement with those of some authors[8 14] and in woeful disagreement with others[1 6]

All possible reasons for the disparity could be placed in one of several categories Differences might arise from geographic or temporal variables—i e studies done in countries with a significantly different cultural and ethnic background—or studies done at a time so far removed that the disease picture may have

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Essentials of Heart Rhythm Analysis Ira W Weiss M D Philadelphia 1973 F A Davis Company 272 pages

The recent interest in cardiac arrhythmia renders this book of value to all who are primarily concerned with care of patients with heart disease Weiss has produced a compendium of strips of ECG recordings which illustrate irregularities in the heart beat which are designed to teach the beginner to interpret cardiac arrhythmias There are many good books available on this subject This publication adds another well planned compendium for training in electrocardiography One hundred unknown tracings are shown in Chapter 6 for the student s study These tracings are then followed by the author s concise explanation of their proper interpretation This is a good feature of the book Students house staff and trainees in cardiology will find this to be a useful publication

Recent Advances in Cardiology Edited by John Hamer M D Ph D Baltimore 1973 The Williams & Wilkins Company 424 pages

Recent Advances in Cardiology is now in its sixth edition and as in the past editions is an excellent publication This edition consists of 16 chapters which review the advances in 16 different fields of cardiology Among these are pediatric cardiology pulmonary embolism bacterial endocarditis, congestive heart failure and shock echocardiology and valve replacement The contributors all except one being from the British Isles have reviewed their respective aspects of cardiology briefly and lucidly The fields of cardiology reviewed, of course were selected A complete review of all aspects of cardiology would be impossible in a relatively small book Nevertheless this is a fine contribution to cardiology The presentations are good the illustrations clear and well selected and the bibliography is also well selected This book represents a valuable course in cardiology and is well worth studying

Neonatal Heart Disease William E Friedman M D Michael Lesch M D and Edmund H Sonnenblick M D New York and London 1973 Grune & Stratton, Inc 299 pages

Friedman Lesch and Sonnenblick have edited and bound in one volume the publications on Neonatal Heart Disease which appeared recently in the *Progress of Cardiovascular Diseases* The title adequately defines the content of this monograph The series of papers are concerned primarily with congenital heart disease They include a discussion of embryology physiology clinical manifestations diagnosis and treatment of neonatal types of heart disease The papers are excellent and although they contain nothing new they do review the common problem extremely well and from the point of view of the practicing pediatric cardiologist This is a valuable publication and certainly worthy of careful study The contributors have included a useful bibliography with each presentation

Cardiovascular Drug Therapy and Iatrogenicity N P Saheta, M D Bombay 1973 Kothari Medical Publications 847 pages

Professor Saheta has produced an important book on cardiovascular drug therapy and adverse reactions His book of over 800 pages reviews for the clinician the commonly used drugs for the management of heart disease It is obvious from the book that Professor Saheta has not only studied the medical literature carefully but had a great deal of personal experience with the drugs discussed It is not possible to describe in detail the contents of this book Nevertheless it contains a discussion of the coronary vasodilators, β adrenergic blocking agents digitalis anti arrhythmic agents anti coagulants hypolipidemic drugs antibiotics, drugs for care of cardiogenic shock and many others This publication reviews extensively the many agents used today in the treatment of cardiac and peripheral vascular diseases. This is a valuable book on cardiovascular therapeutics The presentation is clear and simple It also represents the practical approach to management of cardiovascular disease in India The book is recommended to the clinical cardiologist

Research Communications in Chemical Pathology and Pharmacology Richard J Kones M D Westbury New York 1973 PJD Publications Ltd. 84 pages

Kones has summarized very well the essentials of most 800 publications concerned with altered myocardial contractility As in any brief review 800 reports reduced to 50 pages the data selected for presentation must be limited Nevertheless the author has brought into a supplement to the *Journal on Chemical Pathology and Pharmacology* important information The bibliography is extensive and well selected for those who may wish to investigate the details of the respective reports and problems more extensively The author reviews the molecular and ionic basis of altered contractility from 16 aspects Among the aspects discussed are mechanics of contraction cyclic AMP glucagon, thyroid hormones congestive heart failure and adenyl cyclase energetics sliding filament model Na K and Ca ions digitalis and others This is a good publication on an important subject which is thought provoking It should interest pathologists physiologists, and pharmacologists concerned with muscle disease

mented by elegant stereoradiography method and serial block study of the extramural coronary arteries Although he demonstrated an extremely rich intercoronary anastomosis he also observed that in each instance of acute myocardial infarction there was a recent occlusion of a subtending artery and that such occlusions might be present in a recanalized artery or in the lumen or arteries narrowed up to 1 mm indicating that these impaired vessels could deliver sufficient blood to maintain the myocardium until they were acutely occluded. Many of these obscure but important thrombi would not be observed unless a technique was employed which was equivalent to the one used by Fulton [10]

In medical examiners autopsies performed in instances of sudden and unexpected death circumstantially of cardiac origin Spain and Bradess[2] observed an incidence of recent coronary artery occlusion which increased directly with the length of survival In individuals who died within one hour of surmised onset of disease 16 per cent showed an occlusion in those who survived from 1 to 24 hours occlusion was found in 37 per cent and occlusion was present in 54 per cent of those who died after 24 hours This progressively increasing relation between incidence of occlusion and duration of assumed myocardial ischemia permitted the opinion that a thrombus may be a consequence of an infarction

The authors pointedly and repeatedly designated the suspected myocardial disease as myocardial ischemia and confusion arose when others assumed this term was synonymous with myocardial infarction Since these were medical examiners autopsies it is apparent the terminal disease of these individuals was not medically attended. Hence there could not have been clinical documentation of a myocardial infarction and as a myocardial infarct is not recognizable anatomically within six hours from onset by the usual methods of examination it follows that in those individuals who survived up to 6 hours, there could not have been anatomic or clinical documentation of a myocardial infarct If we reexamine the statistical data in the light of this information it is apparent that an unknown number of individuals without occlusion or infarct and who may have suffered electrical deaths were included in the group dying within one hour a lesser number were included in the group living from 1 to 24 hours and the least were in the group surviving at least 24 hours This could readily explain the statistical increase in coronary artery occlusion associated with an increase in survival Furthermore since a myocardial infarction could not be documented by any means in the individuals surviving less than six hours the statistical data presented by Spain and Bradess[2] do not describe the relationship of occlusion to infarct but more appropriately describe the incidence of coronary artery occlusion in sudden and unexpected death circumstantially of cardiac origin

Recently Erhardt and colleagues[7] in an imaginatively designed study injected ^{125}I labelled fibrinogen into patients hours after the onset of a myocardial infarction at autopsy in those who died, they showed radioactivity in all portions of the thrombus in six of seven instances In order to explain the incorporation of the fibrinogen in the central and distal portions of the thrombus the authors concluded that the thrombus probably formed subsequent to the infarct

There is reason to suspect that their data included the effects of unappreciated factors which would invalidate their conclusions Occluding coronary artery thrombi are usually formed at sites of severe luminal narrowing and it is particularly at these sites that there is a well developed system of vasa vasorum which channels blood from the lumen above the narrowing to the lumen below it In the event of an episodic occlusion of the narrowed segment the vasa vasorum could deliver ^{125}I labelled fibrinogen distal to the occlusion and since the blood flow at this site would be diminished, the radioactive fibrinogen delivered by the vasa would not be significantly diluted nor rapidly washed away and could coat the distal surface of the occlusion In addition there is ample evidence that a thrombus is precipitated on an eroded intima [8,9,14,16,19] and a network of vasa vasorum is consistently present at the periphery of the erosion [20] It is therefore apparent that a vascular mechanism would be available to deliver radioactive fibrinogen to all parts of the thrombus even if it had formed before the fibrinogen was injected. Furthermore a coronary artery thrombus must not be totally occlusive to precipitate a myocardial infarction All that is required is an episodic reduction of the blood flow

differed in detail Or else the differences in observations might stem from differences in definition, materials, or methods of examination From a careful review of all available reports on the association of recent coronary artery occlusion and acute myocardial infarction, I[15] was able to exclude all reasons for the disparity except those which might arise from differences in definition or the methods of examination

There is evidence to support this conclusion In 1956 Branwood and Montgomery[1] reported an association of 36 coronary artery occlusions in 61 instances of myocardial infarction In 1970 Bouch and Montgomery,[16] reporting from the same department repeated the study using a totally different technique to examine the coronary arteries They found an association of recent coronary artery occlusion in 88 per cent of the instances of myocardial infarction and the authors state that ' technique was undoubtedly a major factor in securing so high an incidence of occlusion [16] Since it was in part the observation of a low *association of occlusion and infarct* that prompted Branwood and Montgomery to be the first to suggest that the thrombus may be a consequence of the infarction it is especially noteworthy that a later study from the same department co authored by one of the original authors using a different technique of examination, reports a meaningful *higher statistical* association of occlusion and infarct.

Ehrlich and Shinobara's[4] *meticulously* performed study is frequently cited to support the opinion that a thrombus may be a consequence of an infarct They reported an association of recent coronary artery thrombosis in 50 per cent of acute myocardial infarcts Under the heading of infarcts they include the unicentric type, in which most or all of the acute disease was confined to a circumscribed area often transmural in the left ventricle ' as well as the 'multicentric type—in which there was no zonal concentration of necrosis but widely scattered irregular foci mainly subendocardial, sometimes involving most and occasionally all of the left ventricle as well as scattered areas in the other chamber '[4] The authors obviously combined subendocardial necrosis with transmural infarcts as a single entity A rereading of their report with this blurring of definition in mind *reveals a totally new* situation Only two coronary artery occlusions were associated with 20 instances of subendocardial *necrosis* while *with 18 transmural infarcts* there were 17 associated coronary artery thrombi Since the problem to be resolved is the statistical association of recent occlusion and acute transmural myocardial infarct it is obvious that the conclusions of Ehrlich and Shinobara[4] are invalidated because of an incorrect definition

Branwood and Montgomery[1] reported that the *estimated age of the coronary artery thrombus* was less than that of an associated infarct and therefore the infarct probably caused the thrombus Baroldi[5] reported similar findings These observations could not be confirmed by others. Some authors[4,6,15] did not think there were adequate criteria to permit accurate dating of a thrombus while others[2,16,17] were impressed by the frequent finding of multiple episodes of thrombus formation often days apart which were only revealed by longitudinal section or serial cross section of the entire thrombus If these methods are used, areas are found which are *coeval with the infarct* One or more chance cross sections may only show a more recent episode which might not be coeval with the infarct, and data developed in this manner would lead to incorrect conclusions

Baroldi [5] on the basis of his injection studies of the coronary arteries, proposed the hypothesis that the intercoronary anastomosis could adequately compensate for the potentially ischemic effects of a *recent occlusion of an extramural* branch of a coronary artery and that a coronary artery thrombus was an inconstant consequence of a myocardial infarction

The existence of an extensive intercoronary artery anastomosis has been appreciated since 1907[6] it was always assumed that the minor inconsistencies in anatomic relationship between occlusion and infarct were probably due to the *vagaries of this anastomotic circulation* Except for the infrequent instances of recent occluding coronary artery thrombi (of more than six hours duration) without an associated acute myocardial infarction there is no documentation that the extensive intercoronary anastomosis can compensate within 30 minutes (the estimated time for ischemic necrosis to occur) for episodic and severe reduction of blood flow in the extramural coronary arteries Fulton[10] investigated the coronary artery circulation at postmortem with an injection technique comple

dition if the stasis of blood plus the release of thrombogenic material were to cause arterial thrombi they would certainly precipitate venous thrombi and coronary venous thrombi are not an associated finding of myocardial infarction

Conclusion

Recent studies have purported to show that a cause effect relationship between recent coronary artery occlusion and acute myocardial infarction does not exist but that the infarct precedes and precipitates the associated arterial thrombus The major arguments submitted to support this opinion have been described and reasons have been presented to show that these arguments are critically flawed In addition the proposed hypothesis of primary infarct with subsequent thrombus cannot explain certain consistent anatomic findings which indicate that the coronary artery occlusion precedes and causes the associated myocardial infarct

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for at least 30 minutes, to levels below that required to maintain the myocardium This reduction can be precipitated by a partially occluding thrombus which could grow by accretion after the infarct had become manifest This would be an additional mechanism for permitting the radioactive fibrinogen to be deposited on all portions of the thrombus after the formation of the infarct, a similar effect would result from the retraction of the thrombus from the arterial wall [10] which would allow some blood to trickle through Since the authors did not appreciate these possible pathways for the delivery of radioactive fibrinogen to all portions of the thrombus hours after the infarct had formed, the conclusions they drew from their data are seriously flawed

Most of the authors who reject the view that an acute infarct is caused by a recent coronary artery occlusion have proposed a possible pathogenesis for the infarct They are essentially similar and envision a focal myocardial necrosis which causes a reduction of blood flow to the injured area which in turn causes additional necrosis This process continues in a centrifugal fashion until the myocardial necrosis is sufficiently large to be characterized as an infarct It is then assumed that this infarct would retard the blood flow in a subtending branch of an extramural coronary artery and occasionally precipitate a thrombus A contributory factor might be thrombogenic substances released from the infarct The myocardial lesion which would result from this pathogenetic scheme would be zones of necrosis haphazard in distribution usually multifocal involving the right as well as the left heart showing many progressive zones of necrosis spreading centrifugally possibly sprinkled with multiple thrombi in small intramural vessels precipitated by the locally retarded blood flow consequent on each exacerbation of necrosis These lesions would be totally unlike the transmural infarcts seen at autopsy These are well outlined, at least 2 5 cm in length and width involving at least one half the thickness of the ventricular wall frequently revealing one and rarely more than three episodes of necrosis unusually showing thrombosis of small intramural vessels and rarely involving the right ventricle without necrosis in the contiguous left ventricle Furthermore the transmural infarcts are repetitively seen in certain selected areas of the heart.

The validity of the hypothesized cycle of focal myocardial necrosis (leading to local stasis which causes additional necrosis) can be readily evaluated in myocytolysis[21] and in subendocardial necrosis In these two anatomic entities, the myocardial changes truly fulfill all the pre conditions to set in motion the chain of events hypothesized by those who claim that the infarct precedes the thrombus In both of these entities there are multifocal zones of necrosis scattered throughout the left and right heart. In myocytolysis they are minute and bland while in subendocardial necrosis they are usually larger and associated with an acute reaction In neither entity is there a progression of the foci of necrosis to a transmural myocardial infarct

There are two consistent anatomic findings in myocardial infarction which are probably of pathogenetic importance and cannot be explained by any hypothesis which assumes that the infarct preceded the thrombus One is the intimal erosion beneath the thrombus and the other is the distribution of the thrombus in relation to the infarct

Coronary artery thrombi are precipitated on an eroded intima ruptured by a vector of force which proceeds from the arterial wall toward the lumen [18,24] This consistent change which is probably the immediately precipitating cause of a thrombus cannot be explained by slowing of the blood stream or the myocardial necrosis and the proponents of the primacy of the infarct either do not discuss the role of the intimal erosion[1,3,5,6] or else deny its existence [17] Similarly, the relationship of thrombus to infarct refutes the hypothesis of infarct causing thrombus The distal border of an occluding coronary artery thrombus is separated by 1 to 2 cm of uninvolved artery from the closest margin of anterior and lateral wall infarcts and by 1 to 5 cm from posterior and diaphragmatic wall infarcts and the thrombus is almost always in a subtending vessel If the infarct antedated and caused the thrombus, some of the thrombi as a matter of chance would be directly contiguous or even within the confines of the infarct and the distribution of the thrombus would not be so consistently in a subtending branch but would be scattered around the periphery of the infarct In ad

after the attacks The serum enzymes were normal A twelve lead electrocardiogram recorded every 30 seconds during 10 minutes of atrial pacing at 150 beats per minute did not show any modifications A second selective coronary arteriogram demonstrated a 40 per cent to 50 per cent narrowing of the proximal right coronary artery (Fig 3) The other coronary lesions were unchanged An element of added spasm of the right coronary artery at the previous examination was suspected Unexpectedly the left ventricular angiogram showed a subaortic hypertrophic stenosis confirmed by the demonstration of 75 mm Hg left intraventricular pressure gradient during isoproterenol infusion A right aortocoronary vein bypass and muscular resection of the interventricular septum were carried out The myectomy resulted in a complete atrioventricular block and septal perforation and the patient did not survive the intervention

Case No 3 Mr G R a 53 year old mechanic with a negative previous history was hospitalized in August 1970 He had severe angina on exertion since the fall of 1969 and at rest since May 1970 Physical examination showed a faint aortic systolic murmur The electrocardiogram and chest roentgenogram were normal A selective coronary arteriogram showed a normal left coronary artery On the proximal third of a dominant right coronary artery a curvilinear shadow presumably representing an intraluminal atherosclerotic plaque surrounded by radiopaque material was present (Fig 4) The extent to which this plaque restricted coronary blood flow was difficult to assess Left ventricular angiography was normal After 14½ minutes of atrial pacing at a rate of 150 beats per minute anginal pain occurred and was associated with a marked inferior wall subepicardial current of injury on the electrocardiogram (Fig 5A and B) The pain and electrocardiographic abnormalities disappeared within two and a half minutes after cessation of pacing A right aortocoronary bypass operation was performed in September 1970 Intraoperative vein graft flow was 60 ml per minute and increased to 360 ml per minute after local administration of papaverine Following the intervention, the electrocardiograms showed an inferior wall myocardial infarction confirmed by a marked elevation of serum enzymes Vein graft occlusion was strongly suspected However angiography was not carried out postoperatively and the patient has not returned for follow up examinations

Case No 4 Mr L P a 55 year old steel worker with a previous history of duodenal ulcer in 1964 experienced frequent anginal attacks at rest and occasionally during exercise since January 1972 Following progressive aggravation of his symptoms, the patient was hospitalized in July 1972 On repeated occasions the electrocardiogram showed, during anginal attacks a marked anterior wall subepicardial current of injury associated with supraventricular arrhythmias (premature contractions and/or tachycardia) Between the attacks, the electrocardiogram showed anterolateral subendocardial ischemia The clinical and roentgenologic examinations were normal Selective cinecoronary arteriography showed a severe 80 per cent narrowing of the anterior descending coronary artery between the origin of the first septal and first diagonal branches a 50 per cent proximal narrowing of the diagonal branch a 40 per cent narrowing of the proximal circumflex artery and atherosclerotic irregularities of the proximal two thirds of the right coronary

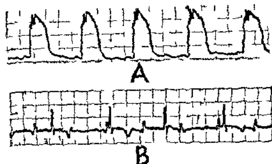


Fig 1 A and B Electrocardiographic modifications during spontaneous angina in case No 1 The tracing (Lead V_3) in A shows the typical marked subepicardial current of injury The tracing (Lead II) in B shows complex atrioventricular dissociation presumably secondary to atrioventricular block (atrial rate faster than ventricular rate)

artery The left ventricular angiogram showed moderate hypokinesia of the anterior wall of the left ventricle An aortocoronary saphenous vein bypass to the anterior descending artery was performed. Intraoperative vein graft flow was 100 ml per minute and flow increased to 240 ml per minute after local administration of papaverine

An anteroseptal myocardial infarction occurred during the early postoperative period Occlusion of the vein graft and proximal anterior descending coronary artery were demonstrated angiographically The occluded artery was opacified distally from a homolateral and contralateral collateral circulation On the left ventricular angiogram anteroapical akinesia was noted postoperatively However the patient continued to experience spontaneous anginal attacks associated with a transient myocardial injury pattern of the electrocardiogram

Case No 5 Mr K T a 44 year old manual worker with an otherwise negative previous history had experienced on two occasions in 1966 and 1968 episodes of retrosternal chest pain radiated to both arms the character of which was poorly defined He was first seen in July 1969 following a recent episode of chest pain accompanied by prolonged supraventricular tachycardia at a rate of 160 beats per minute (Fig 6) The electrocardiogram was normal after the episode Similar anginal attacks without palpitations recurred the following days The attacks occurred at night except on two occasions when they were induced by exertion The patient was again seen in April 1970 following a new anginal episode The clinical and roentgenologic examinations of the heart were normal

During two standard exercise stress tests in the absence of pain, the electrocardiogram showed a diffuse anterior wall subepicardial current of injury which disappeared within a few minutes (Fig 7) The selective coronary arteriogram was normal (Fig 8) except for slight spasm near the origin of the right coronary artery relieved by nitroglycerin. The left ventricular angiogram was normal

The subsequent course was satisfactory However the patient continued to experience short bouts of angina on exercise during periods of a few days separated by free intervals of a few months

Clinical communications

The variant form of angina Diagnostic and therapeutic implications

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Prinzmetal s variant angina[1,2] is relatively fre quent and should be ruled out in patients pre senting severe nonexertional or unstable angina During spontaneous attacks the electrocar diogram distinctly shows a high transient subepicardial current of injury and frequent ar rhythmias [1-13] Discrepancies between this often threatening cinical situation and the findings at coronary arteriography, as well as unpredictable results obtained following aortocoronary sa phenous vein bypass, have prompted the pre sent report

Case reports

Case No 1 Mr L G a 43 year old mechanic was hospi talized in January 1970 He had had severe angina since March 1969 first on exertion then at rest during the last three months Previous history was negative Physical ex amination showed only a faint mesosystolic ejection mur mur The electrocardiogram and vectorcardiogram were nor mal Cardiac fluoroscopy revealed a small proximal left cor onary artery calcification Selective cinecoronary arteriogra phy[14] showed two separate approximately 40 per cent nar rowings on the pre marginal portion of a dominant right cor onary artery a 50 per cent narrowing of the anterior de scending artery between the first septal and first diagonal branches and a 60 per cent narrowing of the posterior divi sion of the marginal circumflex artery Left ventricular angiography was normal Cardiac output and left ventricular end diastolic pressures were normal at rest and following six minutes of a 40 watts supine exercise

In spite of medical therapy the anginal syndrome became worse and the patient was readmitted to the hospital in May 1970 On several occasions during anginal attacks the electrocardiogram showed a marked subepicardial an terolateral current of injury which disappeared following the attack (Fig 1*A*) During one of these episodes an atrio ventricular dissociation presumably secondary to atrio ventricular block (atrial rate faster than ventricular rate) was noted (Fig 1*B*) Between attacks the electrocardiogram was normal On a second cinecoronary arteriogram the 50 to 60 per cent narrowing of the anterior descending coronary artery distal to the first septal branch was again noted (Fig 2*A*) The other coronary lesions were unchanged A vein bypass between the aorta and anterior descending coronary artery was carried out Intraoperative vein graft flow[15] was 90 ml per minute and increased to 210 ml per minute following local injection of papaverine The functional results were satisfactory the patient still having only occasional anginal attacks A hemodynamic study 21 months later showed a patent graft (Fig 2*B*) the coronary lesions were unchanged Following the coronary angiogram the patient complained of severe angina and the electrocardiogram showed a marked anterior wall subepicardial current of in jury The pain was rapidly relieved by two nitroglycerin tablets the electrocardiogram returned to normal and re mained normal thereafter

Case No 2 Mrs S K a 49 year old housewife with a pre vious history of hypertension since May 1969 had recurrent anginal attacks exclusively at rest usually at night since September 1969 She was admitted twice to another hospital in August and September 1971 with angina at re t associ ated on three occasions with syncopal attacks immediately following the intake of nitroglycerin During the last epi sode a partial transient atrioventricular block (episodes of Wenckebach phenomenon) was noted A selective coronary arteriogram in October 1971 showed a 60 per cent narrow ing on the proximal third of a dominant right coronary ar tery and a 30 per cent proximal narrowing of the anterior descending artery

Following progressive aggravation of her angina the pa tient was referred to us and hospitalized in December 1971 Physical examination and cardiac auscultation were nega tive Roentgenologic examination of the heart showed slight left ventricular enlargement There were no coronary calcifications During at least two anginal attacks the electrocardiogram showed an inferior wall subepicardial cur rent of injury The electrocardiogram was normal before and

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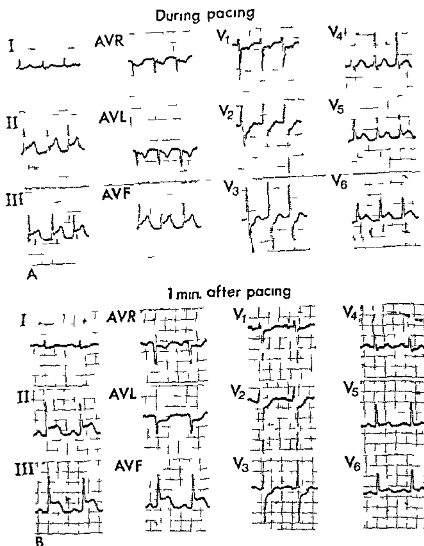


Fig 5 A and B Atrial pacing stress test in case No 3 Marked inferior wall current of injury associated with anginal pain at 15 minutes of pacing (A) and one minute after cessation of pacing (B) The electrocardiogram returned to normal two and a half minutes after cessation of pacing

electrocardiograms without angina during standard exercise stress tests. Another patient (case No 3) has manifested typical angina with an electrocardiographic subepicardial injury pattern during a standard pacing stress test In addition the electrocardiogram frequently shows during anginal attacks a variety of arrhythmias such as supraventricular or ventricular premature beats different degrees of atrioventricular block atrial fibrillation ventricular tachycardia and fibrillation Atrioventricular blocks (cases No 1 and 2) and supraventricular tachycardia (cases No 4 and 5) were documented in our patients.

Prinzmetal and associates[1] originally postulated that variant angina was due to segmental proximal spasm with transient occlusion of a severely stenosed coronary artery This hypothesis has attracted many followers and logically explains several aspects of the syndrome Acute coronary occlusion followed by myocardial necrosis is typically associated with subepicardial injury and frequent arrhythmias Experimentally temporary coronary occlusion induces intense subendocardial vasodilatation and hyperemia with ischemia of the subepicardial layers of the myocardium [1,16]

However many clinical observations in pre



Fig 2. A and B Cineangiograms in case No 1 A Preoperative left coronary arteriogram in the lateral projection showing approximately 50 per cent narrowing of the anterior descending coronary artery (*arrow* ⟶) and 60 per cent narrowing of the posterior division of a small marginal circumflex artery (*arrow* ⟶) B Selective angiogram (frontal view) showing a patent vein graft to the anterior descending coronary artery 21 months after operation



Fig 3 Preoperative right coronary arteriogram (left anterior oblique view) in case No 2 showing 40 to 50 per cent narrowing of the proximal third of the artery (*arrow* ⟶)

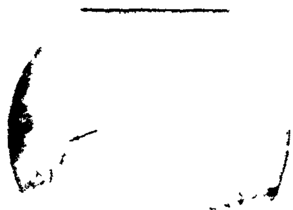


Fig 4. Preoperative right coronary arteriogram (left anterior oblique view) in case No 3 The right coronary artery is dominant and shows on its proximal third a curvilinear shadow presumably representing an intraluminal atherosclerotic plaque surrounded by radiopaque material (*arrow* ⟶)

Discussion

Since the advent of coronary care units and continuous electrocardiographic monitoring the variant form of angina described by Prinzmetal is being recognized more frequently The clinical features of the anginal syndrome are not specific enough to allow clear distinction from the more classic form of unstable angina In a limited but exhaustive review of cases Lesbre and colleagues[3] have documented the occurrence of previous typical angina on exercise in 13 patients and the association of anginal attacks at rest and on exercise in three patients In three of our patients (cases No 1, 3 and 4) classic angina on exercise was present initially and was later followed by angina at rest and of longer duration The fifth patient (case No 5) had episodes of chest pain both at rest and during exercise Only one patient (case No 2) had angina exclusively at rest

The electrocardiogram during anginal attacks typically shows a high subepicardial current of injury delineating the area of myocardial ischemia This occurs transiently and is not followed by sustained evidence of myocardial necrosis In some patients the injury pattern can be induced by standard exercise or, more safely by pacing stress tests[6,7] One patient (case No 5) has shown on two occasions strongly positive



Fig 8 A and B Selective coronary arteriogram in case No 5 Left anterior oblique view of the right coronary artery (A) and frontal view of the left coronary artery (B) showing a normal coronary angiogram

remain functional may be less successful in the relief of symptoms and prevention of complications than in patients with classic angina

On the other hand, Guermonprez and colleagues[16] recently reported in 60 per cent of a group of patients or eight of thirteen patients with variant angina good postoperative clinical and angiographic results within a period of follow up of approximately three months Their series included two operative deaths a third death during the second postoperative month and an occurrence of acute myocardial infarction in the territory of the grafted coronary artery in two patients six and seventeen days after operation Seven patients with successful bypass had severe coronary artery lesions and one only had a 30 per cent narrowing of a coronary artery Much longer periods of follow up are needed however these results suggest that patients with severe anatomical obstructions of the coronary arteries may be improved after aortocoronary bypass operations In patients with more trivial obstructions a predominant functional vasoactive component perhaps involving a substantial segment of the artery may be present and may persist after operation At the present time then only patients with high grade proximal coronary lesions should undergo aortocoronary bypass surgery Continued precise and objective assessment of these patients is mandatory

Summary

A variant form of angina was diagnosed during electrocardiographic monitoring in hospital or during stress testing in five patients. One patient had a severe proximal coronary obstruction Three patients also had proximal lesions of a coronary artery but of more questionable significance One patient had a normal coronary arteriogram An aortocoronary saphenous vein bypass was carried out in four patients with severe unstable angina and coronary lesions One patient died at operation of unrelated causes and two patients suffered a postoperative myocardial infarction One patient still has documented attacks of variant angina in spite of a patent vein graft In these patients the result of aortocoronary bypass appears less predictable than in patients with classic angina

Addendum

Since the submission of this manuscript for publication Oliva and co workers[17] have reported a convincing angiographic documentation of repeated coronary artery spasm associated with episodes of variant angina in a 46 year old woman Their report illustrates the variability in site extent, and degree of obstruction during individual attacks On two occasions the spasm occurred diffusely and was seen to extend into the distal right coronary artery and posterior descending artery The authors supported by McAlpin[18] in an editorial in the same issue logically conclude that spasm beyond a proximal obstruction may preclude the use of saphenous vein bypass therapy alone Whether coronary arterial vasodilators could be as they suggest of significant long term benefit as an additional therapeutic measure in these patients remains to be demonstrated.

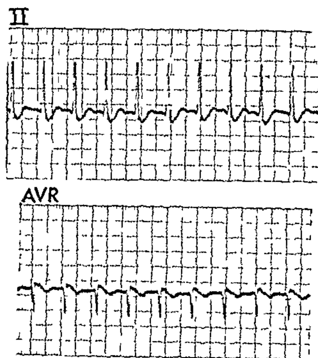
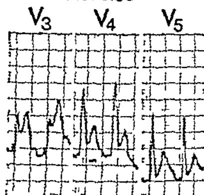


Fig 6 Episode of supraventricular tachycardia at a rate of 160 beats per minute in case No 5 The arrhythmia appeared during spontaneous angina and lasted for several hours after cessation of angina

vious reports and in our patients do not entirely support Prinzmetal s postulate First, it has become obvious recently that the syndrome is not necessarily associated with high grade proximal coronary lesions [8,9] Only one of our patients (case No 4) had a severe (greater than 80 per cent) narrowing of the anterior descending artery Two patients (cases No 1 and 2) had 40 to 60 per cent narrowings of the coronary artery One patient had a comma shaped lesion protruding into the lumen of the vessel the significance of which was difficult to assess Finally as previously reported [9] one patient had an essentially normal coronary arteriogram During coronary arteriography this patient had a transient spasm of the proximal right coronary artery relieved by nitroglycerin

Secondly, occlusion or bypass of the proximal obstruction does not always result in the disappearance of the syndrome Aortocoronary saphenous vein bypass was carried out in four of our patients with coronary lesions and severe unstable angina One patient had a coexistent hypertrophic subaortic stenosis and did not survive extensive muscular resection of the left ventricular septum In the three other patients excellent intraoperative vein graft flows were recorded In our experience, early vein graft closure is unusual under these circumstances [15]



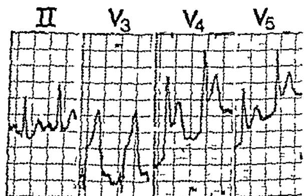


Fig 7 Double Master exercise stress test in case No 5 A typical subepicardial current of injury was seen in Leads V_3 V_4 and V_5 two minutes after onset of exercise The electrocardiogram returned to normal three minutes after cessation of exercise

Nevertheless, two patients had a myocardial infarction during the early postoperative period One patient in spite of postoperative occlusion of a previous 80 per cent narrowing of the anterior descending artery continues to have frequent angina with variant electrocardiographic changes in the same territory [5,10] The only patient who has a patent graft to the anterior descending artery 21 months after operation still experiences mild angina Moreover following a recent angiographic control, we have observed in this patient during an anginal attack a variant electrocardiographic pattern in the anterior wall of the left ventricle

Dhurandhar and associates[12] have recently observed the persistence of variant angina followed by a lethal arrhythmia in a patient with a patent vein graft They suggested that diffuse spasm involving the distal coronary artery may have been responsible for the angina and fatal outcome in their patient. These observations suggest that in these patients, aortocoronary bypass may have a higher risk of failure and even when the grafts

Estimation of central venous pressure by examination of jugular veins

Richard Davison M D *
Richard Cannon M D **
Chicago, Ill.

The central venous pressure as measured at the bedside through a venous catheter with the tip located in an intrathoracic position is a well established method for evaluating venous return and filling pressures of the right side of the heart[1,2] As all invasive techniques it involves discomfort and a small but definite risk for the patient[3,4] Since inspection of the degree of jugular vein distention has traditionally been used to estimate similar aspects of cardiac function the present investigation was undertaken to assess the degree of accuracy with which the central venous pressure (CVP) could be predicted by neck vein examination[5,6]

Methods

Thirty nine seriously ill patients that had had placement of a CVP catheter (Bardic 14 gauge Intracath) were admitted to the study The catheter tip was demonstrated by chest x ray to be in an intrathoracic location proximal to the right ventricle Jugular venous pulses were examined using the method of Lewis[5] End inspiratory and end expiratory estimates for the right and left internal and external jugular veins were recorded. The two investigators made independent observations in each patient and refrained from disclosing their results until after the CVP was measured. The central venous pressure was recorded with the patient supine and the bed flat. For each patient all values were obtained, in rapid succession in a matter of a few minutes

A horizontal plane 5 cm below the sternal angle of Louis was used as the zero reference point[7,8] It is recognized that the ideal location of such reference level remains controversial but since the purpose of this study is to compare data rather than to establish absolute values the issue was avoided by resorting to the same level for both sets of measurements

Results

A total of 128 determinations were made by the two observers in 39 patients Internal jugular veins were frequently difficult to visualize and only 25 values were obtained observation of the external jugular veins resulted in 103 measurements The correlation coefficient between the values obtained by the two observers was 95 the mean difference was 1 08 cm and the standard deviation was ±1 67 cm Considering the CVP as the true measurement the mean error and standard deviation of the values obtained by the clinical observation of the neck veins are summarized in Table I In Table II the same data have been rearranged to indicate the frequency with which different magnitudes of error were observed

In order to demonstrate the degree of scatter observed, in Fig 1 (inspiration) and Fig 2 (expiration) systems of co ordinates were constructed with the measured CVP values displayed on the axis of abscissae and the corresponding estimates obtained by inspection of the external jugular veins were displayed on the axis of ordinates.

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Estimation of central venous pressure by examination of jugular veins

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The central venou pressure as measured at the bedside through a venous catheter with the tip located in an intrathoracic position is a well es tablished method for evaluating venous return and filling pressures of the right side of the heart[1,2] As all invasive techniques it involves discomfort and a small but definite risk for the patient[3,4] Since inspection of the degree of jugu lar vein distention has traditionally been used to estimate similar aspects of cardiac function the present investigation was undertaken to assess the degree of accuracy with which the central venous pressure (CVP) could be predicted by neck vein examination[5,6]

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A total of 128 determinations were made by the two observers in 39 patients Internal jugular veins were frequently difficult to visualize and only 25 values were obtained observation of the external jugular veins resulted in 103 measure ments The correlation coefficient between the values obtained by the two observers was 95 the mean difference was 1 08 cm and the standard deviation was ±1 67 cm Considering the CVP as the true measurement the mean error and stan dard deviation of the values obtained by the clini cal observation of the neck veins are summarized in Table I In Table II the same data have been rearranged to indicate the frequency with which different magnitudes of error were observed.

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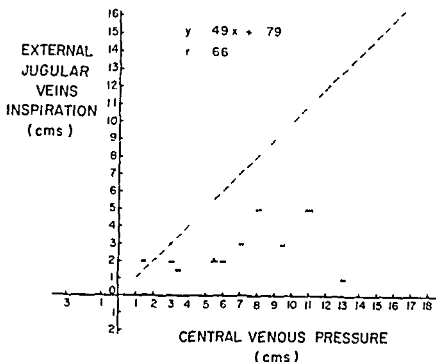


Fig 1 Comparison of the values obtained by examination of the external jugular veins on inspiration and those recorded by actual central venous pressure measurement The correlation coefficient is 66

Table I Mean error and standard deviation from the measured central venous pressure of observations obtained by jugular vein inspection

	Number of patients	*Mean error*	*Standard deviation*
Right external jugular inspiration	22	3 93	5 05
Right external jugular expiration	24	2 64	3 45
Left external jugular inspiration	26	3 29	4 20
Left external jugular expiration	31	2 28	3 09
Right internal jugular inspiration	*5*	*2 02*	*2 41*
Right internal jugular expiration	7	1 72	2 19
Left internal jugular inspiration	6	1 96	2 31
Left internal jugular expiration	7	1 50	2 40

Discussion

Although the number of observations that could be performed on internal jugular veins is too small for adequate analysis it would seem that they are more accurate than the external veins for the estimation of the CVP On the other hand the paucity of values recorded clearly reflects the fact that seldom are the internal jugular pulsations sufficiently obvious to permit measurement Conversely external jugular pulsations were visible in all patients studied but their examination only allowed a rough estimate of the measured CVP Only 47 per cent of the pooled observations were within less than 2 cm of the true value, and in order to obtain a 92 per cent coincidence an error of up to 4 cm had to be allowed Even more significant is the fact that in individual patients wide discrepancies were not infrequently noted (Figs 1 and 2)

Thus two techniques measuring essentially similar parameters of cardiovascular function yield results that are not clinically interchange able If accurate measurement of the central venous pressure is deemed necessary the place ment of an intrathoracic venous catheter ap pears unavoidable

Summary

Attempts were made in 39 seriously ill patients to estimate the central venous pressure

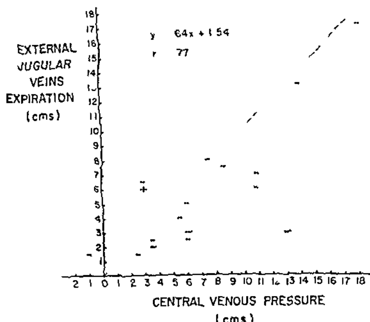


Fig 2 Comparison of the values obtained by examination of the external jugular veins on expiration and those recorded by actual central venous pressure measurement The correlation coefficient is 77

Table II Frequency and magnitude of the error noted when estimating central venous pressure by jugular vein examination*

	Per cent observations with an error greater than		
	2 cm.	*3 cm.*	*4 cm.*
Right external jugular inspiration	68	56 8	30
Right external jugular expiration	56	37	8
Left external jugular inspiration	62	38	21
Left external jugular expiration	39	16	11
Both external jugulars expiration	47	23	8
Right internal jugular inspiration	30	20	10
Right internal jugular expiration	43	7	0
Left internal jugular inspiration	33	8	8
Left internal jugular expiration	14	14	14
Both internal jugulars expiration	38	10	[illegible]

*Data rearranged from Table I.

(measured through an intrathoracic venous catheter) by clinical examination of the jugular veins. Internal jugular veins were usually not visible Inspection of the external jugular veins resulted in 103 measurements These correlated poorly with the actual CVP since only 47 per cent of the pooled observations were within 2 cm of the recorded value To obtain a 90 per cent coincidence an error of up to 4 cm had to be allowed Moreover large discrepancies were noted in individual cases The central venous pressure cannot be reliably estimated by inspection of the jugular veins

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Attempts to reduce arterial thrombosis after cardiac catheterization in children Use of percutaneous technique and aspirin

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Retrograde arterial catheterization is frequently essential in the evaluation of congenital and ac quired heart disease in children One of the most common and serious complications of this techni que is thrombosis of the catheterized vessel The frequency of thrombosis has previously been reported to be 0 3 to 33 per cent using the arteriotomy with open exposure[1 3] and 0 to 3 per cent[1 4-6] using the modified Seldinger per cutaneous technique[7] Many cardiologists feel that percutaneous catheterization is accom panied by a lower incidence of thrombosis[4-6] yet the co operative study on cardiac catheteriza tion[1] revealed a greater incidence of absent pulses when the percutaneous technique was used (1 1 per cent vs 0 3 per cent for open ar teriotomy) Most of those studies have used quite crude methods for evaluation of diminished pulses usually digital examination

In a recent informal survey of 121 pediatric cardiologists there was no general agreement as to which method was preferable[8]

Because in vitro and in vivo work suggest that aspirin may inhibit the formation of arterial thrombi[9 10] a prospective study was undertaken to evaluate if aspirin would influence the inci dence of post catheterization thrombosis and to evaluate the relative merits of open arteriotomy vs percutaneous catheterization in reducing this complication

Material and methods

Ninety five unselected children over 5 years of age hospitalized between June 15 1971 and December 15 1971 for elective cardiac cath eterization were admitted to the study Os cillometric measurements were obtained by the senior author (M D F) using a Collins Sphingo oscillometer prior to and 18 to 24 hours after cardiac catheterization on the catheterized and contralateral extremity The oscillation was recorded as the maximum value obtained deflat ing the cuff from systolic to diastolic pressures

Cardiac catheterizations were performed by a cardiac fellow under the supervision of a staff pediatric cardiologist The decision as to which arterial technique was to be used was made by the catheterizer Percutaneous catheterization was performed using the femoral artery by Seldinger technique as modified by Lurie and col leagues[11] Arteriotomy was performed in the brachial or superficial femoral artery with repair by purse string or interrupted sutures of 6 0 silk Aspirin was given in a dose of 15 mg per kilogram of body weight (maximum 600 mg) once on the evening prior to catheterization three times on the day of catheterization and once the following morning by a random alloca tion technique Neither the person doing the measurements nor the fellow doing the cathe terization was aware of the allocation Although it was apparent which extremity was used for catheterization identical pressure dressings

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arteriotomy diminished pulses occurred with a frequency that was not much different from ours [3,12] and in an oscillometric study of children with open arteriotomies over 85 per cent of children studied had diminished pulses [13]

We would like to emphasize however that when thrombosis occurs with the percutaneous technique it is more likely to be significant because the involved vessel is the common femoral artery and not the superficial femoral or brachial artery which are usually catheterized when open arteriotomy is performed.

The pathogenesis of the thrombosis at the site of catheterization is not completely understood. In the use of the open arteriotomy it has been postulated that (1) a thrombus forms while the vessel is obstructed by the catheter and that it propagates after surgical closure or (2) that during repair of the vessel the lumen is so compromised that stasis occurs and a thrombus forms or (3) that local release of tissue factors causes platelet aggregation and subsequent clot formation The pathogenesis of thrombosis during the percutaneous technique has been attributed to deposition of fibrin along the length of the catheter while it is in contact with blood. When the catheter is removed, the fibrin is stripped off and propagates at the puncture site or embolizes distally This is an attractive hypothesis confirmed by angiographic studies while the catheters are being removed [14] but the effect of local release of tissue factors and/or mechanical factors related to the puncture has not been fully evaluated

We were at first hopeful that aspirin since it does inhibit platelet aggregation would prove beneficial in the prevention of arterial thrombosis That this is not the case suggests that either (1) the mechanism of clot formation during percutaneous or open arteriotomy is mostly mechanical obstruction of the lumen or (2) that the fibrin deposition on the catheter is independent of platelet aggregation or (3) that the step inhibited by aspirin is not the rate limiting factor

Recently Hynes and associates[15] failed to demonstrate an antithrombotic effect from aspirin in 150 adults undergoing coronary angiography by open arteriotomy via the brachial artery They cite as a possible explanation for the failure that the dose of aspirin used may have been inadequate or the timing improper Our study confirms their findings of a lack of aspirin effect in preventing arterial thrombosis In addition the children in our study got a larger relative dose of aspirin for a longer period of time and many were catheterized by the percutaneous technique where local release of tissue thromboplastin may be less

Summary

In an attempt to determine if percutaneous arterial catheterization rather than open arteriotomy or the use of an antiplatelet agent, aspirin would reduce the incidence of arterial thrombosis after cardiac catheterization 95 children were studied. After measuring the amplitude of pulsations by oscillometry on the day of admission the children were randomly divided into two groups One received aspirin 15 mg per kilogram of body weight per dose for 5 doses and the other served as a control Method of arteriotomy—percutaneous or open surgical incision—was left to the discretion of the catheterizer Repeat oscillometric measurements were obtained before discharge

Percutaneous catheterization was associated with a significantly fewer number of diminished pulses ($p = < 0.001$) This effect was most significant in the older children No significant effects on the number of diminished pulses were noted with the use of aspirin

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Table I Oscillometry index (O I) compared to age at catheterization in children with open arteriotomy or percutaneous arterial catheterization*

		Age (yr)			
		5 7	8 12	≥ 13	Total
O I = < 50%/total	Arteriotomy	7/12	2/9	5/9	14/30
	Percutaneous	3/7	4/27	1/31	8/65

Percutaneous catheterization was associated with significantly fewer diminished pulses (P = < 0 001)

Table II Oscillometry index in the group that received aspirin compared to non interventions*

	< 50%	≥ 50%
ASA	8	29
No ASA	14	44
Total	22	73

No significant difference was demonstrated (P = NS)

covered the incision so that the method of pro cedure was not known to the investigators

The change in magnitude of the oscillometry (OSC) reading was calculated using the non cath eterized extremity as a control by the equation

$$\text{Oscillometry Index (OI)} = \frac{100 \times \text{OSC of Index ext (after cath)}}{\text{OSC of Index extrem (before cath)}} \times \frac{\text{OSC of control (before cath)}}{\text{OSC of control (after cath)}}$$

If the OI was < 50 per cent the pulse was con sidered to be significantly diminished Data were analyzed using the group t statistic

Results

Sixty five children were catheterized by the modified Seldinger technique and open arte riotomies were performed in 30 The results are summarized in Table I

The percutaneous technique resulted in a sig nificantly less frequent diminution of pulses (p = < 0 001) This was more striking when re lated to age The pulse diminution was observed in 43 per cent (3/7) in the 5 to 7 age group 15 per cent (4/27) in the 8 to 12 group and only in 3 per cent (1/31) of those over 12 years of age In the group with open arteriotomy there was no dis cernible age trend

Comparison between the group that received aspirin and the control group showed no signifi cant difference in the oscillometric index (Table II), even when other variables such as age or type of procedure were considered In three children the extremity remained cold with poor capillary filling 48 hours after catheterization These 3 had surgical exploration and a clot was removed All were in the group with open surgical arteriotomy and none had received aspirin

Discussion

Our study demonstrates that in our institution the use of percutaneous arterial catheterization is less frequently associated with diminished pulses than is the use of open arteriotomies This is especially true in older children The adminis tration of aspirin did not appear to influence the pulse deficit

Percutaneous arterial catheterization in children has been advocated by many[4-6] but has not been universally accepted for a variety of reasons including difficulty in catheterizing the artery in infants and small children limited catheter maneuverability excessive bleeding at the puncture site, and increased risk of suben docardial extravasation of contrast material with an end hole catheter However with appropriate precautions and adequate experience most of these difficulties can be overcome The less frequent pulse loss after percutaneous ap proach in our group may be because this ap proach depends less on the surgical skill of the cardiologist In other series however with more experienced cardiologists performing the open

Use of droperidol-fentanyl sedation for cardiac catheterization in children

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Since the study by Smith and co workers[1] in 1958 the ataractic mixture of meperidine chlorpromazine and promethazine has been the standard sedation used for cardiac catheterization in children Other combinations including meperidine and hydroxyzine or meperidine and secobarbital have also been employed for this use These combinations have not provided adequate sedation for as many as 50 per cent of older children (over two years) and adolescents in our laboratory as judged by the necessity for giving additional sedation to complete the study with the patient quiet

Therefore a prospective study was undertaken to evaluate the use of Innovar a neuroleptic combination of droperidol and fentanyl as a sedative agent for cardiac catheterization This agent has been used extensively for anesthesia and in large doses can cause profound respiratory depression The purpose of the investigation was to (1) determine if Innovar produces significant respiratory depression or bradycardia in the dose employed, (2) quantify left ventricular performance to determine if depression of contractile function is produced, (3) evaluate the degree of sedation produced, and (4) evaluate possible side effects of the drug combination

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Methods

A total of 106 consecutive children two years of age or over with congenital heart disease who were studied at Vanderbilt Medical Center from Sept. 1 1971 until Jan 1 1973 were included in the study Ages ranged from two to 16 years (The drug is not approved for children less than two years) Twenty five patients were cyanotic with systemic O_2 saturation less than 85 per cent In novar 0 025 c c per kilogram of body weight (maximum dose 1 c c) was given intramuscularly 30 minutes prior to the procedure In 39 patients the drug was given in the catheterization laboratory and heart rate and respiratory rate were taken after the child had been positioned on the cardiac catheterization table Heart rate was obtained from the electrocardiogram (ECG) and respiratory rate was taken for one minute by a nurse Heart rate and respiratory rate were obtained immediately before and following Innovar at 15 30 60 90 120 150 and 180 minutes Many of the patients had left the catheterization laboratory prior to the latter two assessments and therefore both heart rate and respiratory rate at these times were taken by a nurse counting for one minute

The degree of sedation was judged as satisfactory if the patient remained quiet so that the entire procedure could be completed without further sedation Patient reactions occurring within 24 hours of the drug were considered possibly related and therefore listed as side effects

Left ventricular (LV) volumes were calculated from biplane cineangiocardiograms at end diastole and end systole in 33 patients without LV volume overload These patients diagnoses

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Table I Left ventricular volume variables

Patient	Age (yr)	LVEDV (ml/M²)	LVEDV % normal	LVEF	LVSI (L/min/M²)	LVSI % normal	Diagnosis
1 B L	2 5	66	112	0 53	4 17	95	Pulmonary stenosis
2 S N	2 7	66	99	0 76	6 09	132	Small patent ductus
3 J K	2 8	69	97	0 61	4 57	96	Pulmonary stenosis
4 D B	4 3	81	111	0 64	5 92	108	Atrial septal defect
5 B D	4 9	74	103	0 69	5 58	119	Aortic stenosis
6 D T	5	53	76	0 52	3 32	71	Atrial septal defect
7 T L	5	83	112	0 53	3 67	81	Small patent ductus
8 V S	6	82	122	0 73	6 25	137	Atrial septal defect
9 J H	6	51	74	0 51	3 03	66	Atrial septal defect
10 D B	6	81	111	0 63	5 92	108	Atrial septal defect
11 A K	6	79	105	0 67	7 42	162	Aortic stenosis
12 S T	6	58	82	0 75	5 23	112	Pulmonary stenosis
13 R C	7	95	133	0 65	6 50	144	Coarctation
14 R O	7	68	91	0 71	4 46	95	Coarctation
15 P J	7	63	88	0 70	5 34	121	Systemic hypertension
16 J K	7	98	137	0 72	6 60	143	Pulmonary stenosis
17 S B	7	59	83	0 60	3 70	80	Atrial septal defect
18 T N	8	80	122	0 66	4 78	105	Aortic stenosis
19 K S	8	80	109	0 65	5 10	110	Coarctation
20 M C	9	77	99	0 64	4 03	88	Atrial septal defect
21 B M	9	72	97	0 57	3 89	86	Pulmonary stenosis
L J	9	53	76	0 74	5 25	116	Normal heart
3 E F	9	82	118	0 71	6 67	139	Coarctation
24 A C	9	74	100	0 78	6 80	149	Coarctation
25 E G	10	62	80	0 90	4 41	99	Aortic stenosis
26 K L	10	82	110	0 60	6 36	144	Ebstein s Disease
27 J H	10	60	85	0 71	4 86	107	Partial anomalous pulmonary venous connection
28 J S	10	69	93	0 74	4 42	96	Coarctation
29 S M	13	101	127	0 77	5 83	152	Pulmonary stenosis
30 J B	13	82	108	0 67	4 13	97	Normal heart
31 M H	13	79	106	0 75	7 04	160	Aortic stenosis
32 V W	14	61	79	0 72	5 05	126	Post operative anomalous coronary artery
33 B H	14	66	83	0 80	4 [illegible]6	118	Aortic stenosis
Mean	7 88	72 9	101 0	0 678	5 18	114 0	
SD†	3 16	12 6	17 1	0 088	1 15	[illegible] 9	

Sy tol c index = LV t ke lum × heart te

$$†SD = \frac{\sqrt{\Sigma(x - \bar{x})^2}}{N - 1}$$

have values for LVEDV which are slightly increased (137 and 127 per cent of normal)

LVEF is ≥ 51 per cent in all patients with an average of 67 per cent. When LVEF was plotted as a function of B S A four patients fell just below the normal range (Fig 3) Twelve patients had ejection fractions which were increased, including seven with LV pressure overload. LVSI was normal or increased in all patients

Left ventricular contractile state Left ventricular contractile state indices are shown in Table II and Fig 4 All indices indicate normal or increased values for myocardial contractility All patients in this group have normal LVEDV and wall mass

Degree of sedation Adequate sedation generally was achieved within 15 minutes of drug administration with the patient going to sleep but being easily arousable Sedation had to be supplemented in only two patients with

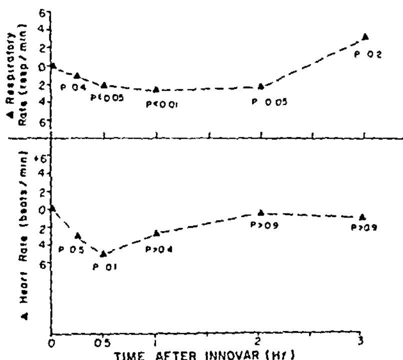


Fig 1 Mean values for changes in respiratory rate and heart rate following Innovar

included atrial septal defect coarctation of the aorta aortic stenosis pulmonary stenosis systemic hypertension small patent ductus with left to right shunt < 35 per cent of pulmonary flow, Ebstein s disease normal left heart, post operative anomalous origin of a conus coronary artery and partial anomalous pulmonary venous connection (Table I) The details of the methods for volume calculations have been reported pre viously [2,3] Left ventricular function was evalu ated by comparison of left ventricular end diastolic volume ejection fraction and systolic index with normal values [3]

Left ventricular pressure (P) was measured with a catheter tip transducer* in seven patients with either atrial septal defect mild aortic stenosis, pulmonary stenosis coarctation or small patent ductus These patients had normal LV end diastolic volumes and LV wall mass In addition their ages and heart rates were not different from a previously described normal group [4] Left ventricular pressure-velocity indices of myocardial contractile state were calculated Calculated values for the Vmax index were derived during isovolumic systole by plotting (dP/dt)/28P as a function of P and (dP/dt)/28 (P Po) vs P–Po (where Po = end diastolic pressure) Contractility indices derived were maximal (dP/dt)/28P, Vmax index using total pressure (P) Vmax index using developed pressure (P-Po) ≥ 10 mm Hg, and Vmax index using developed pressure ≥ 5 mm Hg The details of this method and normal values for comparison have been re ported previously [4]

*Model No PC 350 5F Millar Instruments Hou ton Texas

Results

Effect on heart rate and respiratory rate Fig 1 shows mean values for changes in heart rate and respiratory rate following Innovar There were no significant alterations from control values for heart rate and only small decreases in respiratory rate at 30 60 and 120 minutes The decrease in respiratory rate averaged less than three per minute There were no individual in stances of substantial decreases in heart rate or respiratory rate which required stimulation or drug therapy Systemic oxygen saturation in acyanotic patients was determined and was ≥ 92 per cent in all patients while breathing room air In addition arterial PCO_2 was measured in 12 pa tients and was < 38 mm Hg

LV volume studies Left ventricular end diastolic volume (LVEDV) ejection fraction (EF) and systolic index (LVSI) are shown in Table I for patients without ventricular shunts and without left sided valvular regurgitation The mean values for all variables are not significantly different from normal (p > 0 5) Individual values for LVEDV as a function of B S A are shown in Fig 2 Two patients with pulmonary stenosis

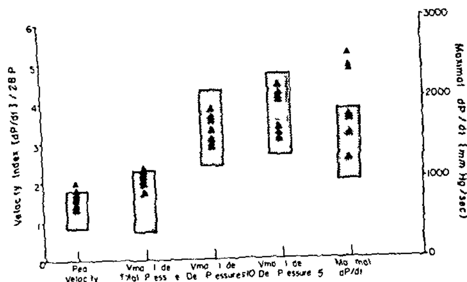


Fig 4 Left ventricular contractile state indices (following Innovar sedation) for seven patients with normal end diastolic volumes and wall mass

Table II Left ventricular contractility indices in patients with normal left hearts

Patient	Diagnosis	Age (yr)	Heart rate	Max dP/dt (mm Hg/sec)	Peak Vce (sec⁻¹)	Vmax index total pressure (sec⁻¹)	Vmax index Dev Pr ≥ 5 (sec⁻¹)	Vmax index Dev Pr ≥ 10 (sec⁻¹)
1 S N	Small PDA	2 5	119	1 575	1 828	2 078	3 160	3 037
2 D B	ASD	4 3	115	2 554	1 988	2 30[illegible]	4 172	3 663
3 B D	Mild AS	4 9	83	1 773	1 610	2 168	4 538	3 648
4 A C	Coarctation	8 5	92	1 743	1 394	1 739	2 972	2 847
5 J N	ASD	12 0	92	2 437	1 578	2 152	4 143	3 768
6 M H	Mild AS	12 5	97	2 387	1 605	2 199	3 292	3 252
7 S M	PS	13 0	52	1 227	1 478	2 339	4 007	2 958
	Mean	8 2	93	1 957	1 64	2 14	3 75	3 31
	±SD	4 4	22	505	0 204	0 198	0 603	0 374

Abbreviations V ce = contractile element velocity = (dP/dt)/28P Dev Pr = developed pressure PDA = patent ductus arteriosus ASD = atrial septal defect, AS = aortic stenosis PS = pulmonary stenosis

Five patients developed nausea during catheterization Four of these instances occurred following contrast medium injection

Discussion

Over the past year we have found Innovar to provide safe effective sedation for children undergoing cardiac catheterization The onset of action is rapid and the degree of sedation is adequate without production of significant hypoventilation or cardiovascular depression in the dose employed. The patient is easily aroused, but if undisturbed is usually quiet The duration of sedation generally is from two to four hours

In the 33 patients studied in whom left ventricular volumes were calculated end diastolic volume was normal in all but two The slight increase in LVEDV in one patient with pulmonary stenosis is probably related to his slow heart rate (52 per minute) The increase in LVEDV in the remaining patient is unexplained, but is not felt to represent depressed myocardial function since the ejection fraction was normal

The LV ejection fraction for the entire group was normal Four patients had LV ejection fractions which were slightly below the lower limits of a regression equation derived from patients with normal left hearts None had ejection frac

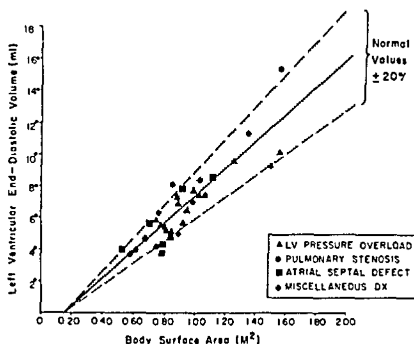


Fig 2 Left ventricular end diastolic volume as a function of body surface area for patients (with Innovar sedation) without left heart volume overload Normal values indicated by the shaded area

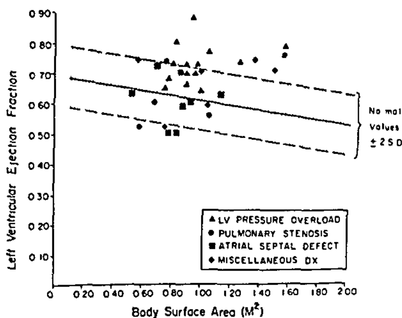


Fig 3 Left ventricular ejection fraction (with Innovar sedation) as a function of body surface area

Demerol 1 mg per kilogram of body weight in one instance and Innovar 0 012 c c per kilogram of body weight in the other These drugs were given 1 5 and 2 hours after the initial dose Sedation usually lasted for two to three hours without apparent decrease in the degree of sedation present

Side effects One patient age 4½ years, developed athetoid involuntary movements associated with a blank stare and unresponsiveness to command *three* hours following the finish of the catheterization procedure and five hours following drug administration There were no tonic or clonic movements associated with this reaction and the patient's mental status and muscle activity returned to normal approximately five minutes after intravenous diphenhydramine (Benadryl)

Three patients developed uncontrolled shivering during the catheterization procedure prior to contrast medium injection and *without* associated drop in body temperature The shivering diminished in each instance following intravenous diphenhydramine

doses >0 025 c c per kilogram of body weight (maximum 1 c c) and therefore would not recommend exceeding this dose

Summary

Droperidol fentanyl sedation for cardiac catheterization was evaluated in 106 consecutive children ≤ two years of age The dose of 0 025 c c per kilogram of body weight (maximum 1 c c) produced adequate sedation in all but two patients without producing significant hypoventilation or heart rate changes In patients without left heart volume overload or myocardial disease left ventricular volume studies and pressure velocity indices of contractile state were normal Side effects were rarely encountered and easily controlled or reversed with diphenhydramine Although we recommend this combination for cardiac catheterization sedation we would not recommend exceeding our dosage schedule

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Table III Sedation effectiveness and side effects
Total number of patients = 106

	Number	%
Additional sedation required	2	1 9
Athetoid movements	1	0 9
Shivering	3	2 8
Nausea before contrast media	1	0 9
Nausea after contrast media	4	3 8

tions below 0 50 Two of these patients had atrial defects with end diastolic volumes which were small (74 and 76 per cent of normal) and thus this decrease in preload could account for a slight decrease in LVEF without considering depressed LV function Of the remaining two patients, one had pulmonary stenosis and the other a small patent ductus arteriosus Neither patient had an abnormal LVEDV and these borderline low values for the ejection fraction probably do not indicate abnormal cardiac function

Several investigators have studied the effect of fentanyl and droperidol on myocardial function in animals Strauer[5] showed that concentrations of fentanyl of 1 0 μg per milliliter produced no significant effect on contractility of cat papillary muscle If the drug were injected intravenously in patients and distributed only in plasma volume (assumed = 5 per cent of body weight) peak plasma concentration would be 0 025 μg per milliliter or less for any child with our present dose (0 00125 mg per kilogram of body weight of fentanyl)

Droperidol produces a mild transient fall in blood pressure (7 to 10 per cent) a decrease in femoral vascular bed resistance and no change in cardiac output with intravenous doses of 0 25 mg per kilogram of body weight or greater in anesthetized dogs[6] In addition this dosage decreases the pressor response to intravenous epinephrine Our dose of droperidol (0 0625 mg per kilogram of body weight) is one fourth this animal dose When the combination of droperidol and fentanyl in a dose similar to our patient dose (50 and 1 μg per kilogram of body weight) was injected intravenously in anesthetized dogs there was a mild transient decrease in blood pressure no change in heart rate, a decrease in femoral arterial resistance, and a decreased pressor response to epinephrine[7] Thus these animal studies suggest that minimal or no changes in contractile state would be expected in children with our current dose regimen The present study showing normal contractile state indices in seven children indicates that this drug combination does not importantly influence contractile state under these conditions Further studies appear indicated in regard to possible partial alpha adrenergic blockage and effects of the drug combination on systemic and pulmonary vascular resistance

Susmano and colleagues[8] have compared the effects of Innovar (in a dose almost 100 times greater than the dose used in our study) with pentobarbital on the acute production of hypoxic pulmonary hypertension in dogs These authors found that over 40 per cent of 22 dogs receiving pentobarbital did not show pulmonary arterial hypertension with hypoxia, whereas all animals receiving Innovar did have reactive pulmonary beds with hypoxia Control pulmonary arterial pressures and resistance measurements were normal in the Innovar group Goldberg and associates[9] have demonstrated that both the meperidine promethazine chlorpromazine sedative combination and a meperidine hydroxyzine[10] combination cause significant alterations in pulmonary and systemic vascular resistances in the intact unanesthetized dog These findings suggest that Innovar may be a more useful cardiac catheterization sedation combination if indeed it does not alter pulmonary resistance or reactivity in children

Side effects associated with Innovar were rarely encountered in this study and involuntary movement disorders responded to intravenous diphenhydramine There were no instances of hypoxic spells occurring in cyanotic patients

These data indicate that the neuroleptic combination of droperidol and fentanyl in the dose of 0 025 c c per kilogram of body weight provides adequate sedation for cardiac catheterization in children without depression of myocardial contractile state The low incidence of side effects coupled with the usual predictable degree of light sedation has made this combination the preferred premedication for children in our catheterization laboratory It should be emphasized that higher doses which have been used for anesthesia may cause significant respiratory depression We do not have any data with the use of

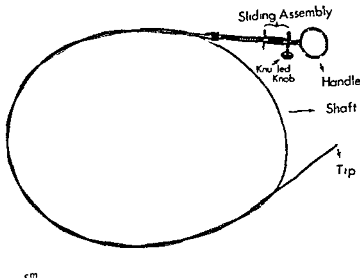


Fig 1 Biopsy catheter See text for detailed description.



Fig 2A Endomyocardial biopsy specimen (under low power) *E* Endocardium *M* myocardium

the catheter tip the biopsy specimen was not obtained until it had been made certain by means of an intracardiac electrocardiogram recorded from the catheter and by premature beats of left bundle branch block type resulting from contact of the catheter s tip with the endocardium, that the tip was in the right ventricle It was further made sure that the sinus beats during the initial contact and pressure of the tip against the endocardium did not develop right bundle branch block morphology thus eliminating the possibility of taking the right bundle and its branches in the biopsy All secured, keeping a constant pressure against the endocardium the tip is opened and closed, thus obtaining the biopsy specimen The catheter is then withdrawn keeping the tip in closed position

In two patients who had very large right atria and in whom there was difficulty in negotiating the catheter through the tricuspid valve into the right ventricle a modified technique was used. Subsequently this modified technique was used

Transvenous endomyocardial biopsy using the gastrointestinal biopsy (Olympus GFB) catheter

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Recently we described our experience with endomyocardial biopsy using Konno s Bioptome[1,2] To date we have used this technique in 27 patients This method is simple and safe to perform Occasionally however, the blood trapped inside the Teflon sleeve of the Konno s Bioptome is difficult to clean out thus making future use of the Bioptome hazardous in terms of febrile reactions In patients with huge right atria sometimes it becomes difficult to negotiate the catheter through the tricuspid valve into the right ventricular apical area It was because of these problems that we started using the Gastrointestinal Biopsy catheter, used with Olympus Gastro Fiberscope and Esophago Fiberscope This communication will describe our experience with endomyocardial biopsy using the Olympus GFB biopsy catheter in 23 patients To our knowledge this will constitute the first reported use of this catheter for endomyocardial biopsy

The instrument

The GFB Biopsy catheter (Olympus) (Fig 1) closely resembles Konno s endomyocardial Bioptome[3] except that there is no Teflon sleeve covering the shaft and that the sliding assembly has only one knurled knob which serves to fasten the sliding assembly Briefly it is a metal catheter which is made of coiled stainless steel wire and therefore quite flexible It measures 130 cm in length and has a diameter of 2 mm Its proximal end bears a handle and a sliding assembly while the distal end carries the biopsy spoons The sliding assembly can be pushed down or pulled up along the long axis of the catheter thus approximating and separating the spoons respectively A knurled knob borne on the sliding assembly can be used to fasten the latter in pulled up or pushed down position The tip consists of two elliptical spoonlike structures with sharp cutting rims They face each other on the concave side Their diameter is 2 5 mm and depth measures 2 mm Through a central connection they are connected to the sliding assembly To facilitate the passage of the catheter across the tricuspid valve the catheter is gently bent into a curve of about 45 degrees approximately 6 cm from the tip

Material and procedure

Twenty five patients with suspected myocardial involvement were selected for myocardial biopsy Their ages ranged from 12 to 70 years 13 were male and 10 were female Clinical diagnoses included primary myocardial disease myocarditis thyrotoxic heart disease and sickle cell cardiomyopathy

Indications for this procedure included heart disease of unknown etiologies particularly those involving the myocardium Any patient capable of undergoing right heart catheterization can tolerate this procedure Patients were prepared as for cardiac catheterization The saphenous vein was used in 24 patients and the external jugular vein in one The tip of the catheter was fixed in closed position The catheter was then introduced into the vein and under constant fluoroscopic control advanced to the right atrium and then into the right ventricle Once there an attempt was made to keep the tip toward the right ventricular apex or its septal surface Because fluoroscopy in the anteroposterior view cannot always distinguish a right ventricular from coronary sinus position of

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specimens measure 2 by 2 5 mm which are ade quate for microscopic examination and bacterial or viral culture studies There have been no im mediate or late complications

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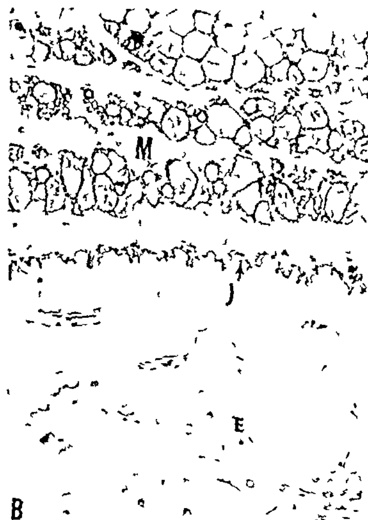


Fig 2B Electron microscopic section showing endocardium and myocardium and J junction between the two

routinely A No 12 Cournand catheter filled with heparinized normal saline was first passed into the saphenous vein and advanced into the right ventricle The tip was pointed toward the desired area of myocardial biopsy The biopsy catheter was then introduced into the Cournand catheter and advanced until the tip protruded out The biopsy was obtained as described previously Several samples could be obtained with relative speed and safety Once the biopsy specimen was brought out, the tip was opened and the specimen put in the proper fixative

Results

Two to three specimens were obtained from every patient The success rate of obtaining specimens was 100 per cent Except for premature ventricular beats of left bundle block morphology at the time of contact of the tip with the endomyocardium there were no immediate or late complications These patients have been followed for from two to 24 months

Discussion

The safety of the technique, the simplicity of the operation the absence of complications and failure the ease with which the instrument can be negotiated through the tricuspid valve either alone or through a No 11 or 12 Cournand catheter already positioned and the simplicity of cleansing out the blood trapped inside the instrument, makes the use of this catheter rather appealing The success rate of obtaining biopsy specimens was 100 per cent as compared to an over all success rate of 88 per cent reported in our previous communication [1] The biopsy specimens are 2 by 2 5 mm in size and can be subjected to light and electron microscopic examinations and other diagnostic and investigative studies [4] Inclusion of the endocardium in the biopsy specimens adds a dimension to the value of the procedure and assists in diagnosing the disease predominantly involving the mural endocardium (Fig 2) The reproducibility of the diagnostic findings from one specimen to another taken from the same patient was very good as suggested by the findings of identical lesions in cases in which multiple specimens were obtained

The occasional difficulty of passage of the catheter through the tricuspid valve into the right ventricular apical area has been solved by first introducing a Cournand catheter (the softness of which allows better manipulation) and positioning its tip in the desired position and then introducing the biopsy catheter through it This technique also avoids any possibility of perforation of the veins and the right atrium

Summary

The use of a GFB biopsy catheter (Olympus) for endomyocardial biopsy in 23 patients is described The catheter may be introduced alone or through a Cournand catheter This technique is simple and safe and has a success rate of 100 per cent There is little problem with cleaning out the blood The technique of introducing the biopsy catheter through an already positioned Cournand catheter avoids any damage to the veins or perforation through the vein or right atrium even in patients with large right atria, the procedure of first manipulating a soft rather than a stiff catheter into the right ventricle and then introducing the biopsy through the Cournand catheter becomes technically easy The biopsy

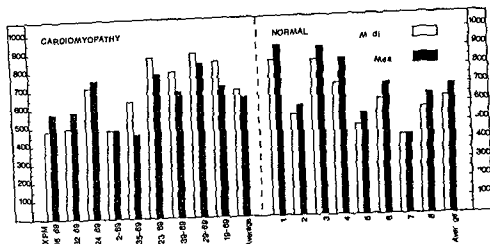


Fig 1 Mean and median size of cardiac muscle fibers in Rhodesian cardiomyopathies compared with normal Rhodesian hearts

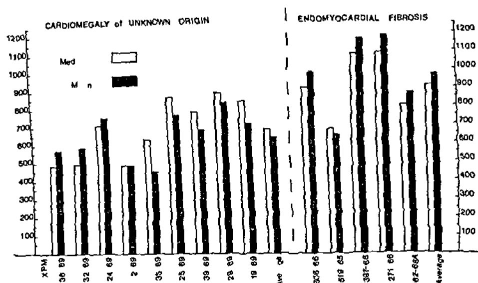


Fig 2 Cardiac muscle fiber sizes in Rhodesian CUO compared with the cases of EMF studied

outlines were transferred to cardboard the same type of cardboard was used for all the photographs The outlines of the cardiac muscle fibers were then cut out and weighed separately a minimum of 250 fibers was taken in each case although most sections contained 300 *to 400* fibers.

Results

The results are shown in Tables I and II and Figs. 1 and 2 In the normal control hearts the muscle fiber size had a mean value of 699 mg and a median value of 628 mg In the cases of CUO studied, the mean value of fiber size found was 647 mg and the median value was 688 mg

Statistical comparison of these two groups of figures shows that there is *no statistically significant difference* and therefore the muscle fibers in CUO are not hypertrophied

In the five cases of EMF the muscle fibers were *larger* The mean size was 973 mg and the median size was 916 mg

Both the mean and median values for cardiac *muscle fiber* size in EMF were higher than in CUO or in controls Statistical analysis ($p<0.05$) showed that the fibers in EMF were hypertrophied When the fiber sizes in CUO are compared with those in EMF ($p<0.01$) it becomes

Cardiac muscle fiber size in African cardiomyopathies

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Spontaneous idiopathic cardiomyopathies occur commonly among the indigenous inhabitants of tropical and subtropical Africa similar cardiomyopathies have been reported from the other tropical and subtropical parts of the world These cardiomyopathies endomyocardial fibrosis (EMF) and cardiomegaly of unknown origin (CUO) are generally considered to be two distinct diseases

This division of the tropical cardiomyopathies was first put foward in detail by a WHO study group[1] but their report being largely clinical, gave no details of the histological changes found in the hearts studied This classification has many supporters[2,3] but other writers[4,5] disagree and believe that these two clinical conditions are simply differing presentations of a single disease process

Many of the original descriptions of the histological differences between these two conditions, such as the absence of elastic tissue in the thickened endocardium in EMF,[6] and the claim that the presence of large amounts of acid mucopolysaccharides (AMPS) in the endocardium and myocardium is specific for EMF[7] are now known to be incorrect Large amounts of AMPS are also found in the intramyocardial connective tissue and thickened endocardium of such cardiomyopathies as endocardial fibroelastosis or ischemic cardiomyopathy

Some workers still maintain that it is possible to differentiate histologically between EMF and CUO because ' the cardiac muscle fibers in CUO are hypertrophied [8] whereas those in EMF are not, but an earlier study of muscle fiber size in CUO, in which direct measurements were made showed them to be of normal size[9] It seems especially important to establish correct measurements because cardiac biopsies are now being carried out to diagnose cases of CUO and EMF[10] and much of their interpretation depends on the presence or absence of hypertrophy of the cardiac muscle fibers In this study the fibers were measured objectively the results did not depend upon a purely subjective interpretation as seems to have been the case in some other writings

Methods

The hearts of nine patients with CUO were obtained from Rhodesia and studied in conjunction with the hearts of five patients with EMF (three from Uganda and two from Ghana) The hearts of eight healthy Africans who had died suddenly in accidents in Rhodesia were used as control The material was received either as entire formalin fixed hearts or as blocks of formalin fixed paraffin embedded tissue

All the cardiac tissue used was taken from a standard site at a point in the lateral wall of the left ventricle 2 cm below the mitral valve The block of muscle taken included the full thickness of the ventricular wall including both pericardium and endocardium

The cardiac muscle was embedded and processed in the usual way and sections were cut at 3 to 4 microns and stained with hematoxylin and eosin The sections were photographed at a standard magnification (×50) and then all these negatives were printed in a similar fashion so that any additional enlargement would be similar in all cases Tracings of the muscle fibers in these photographs were then made and the tracing

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Table II Comparison of cardiac muscle fiber size in CUO and EMF

No	Sex	Age	Heart weight (Gm.)	Cardiac muscle fiber weight (Gm.)	
				Median	*Mean*
CUO—Rhodesia					
XPM 36/69	F	30	440	480	570
XPM 32/69	M	32	410	492	583
XPM 24/69	M	50	880	713	752
XPM 2/69	M	43	490	480	480
XPM 35/69	F	36	420	635	454
XPM 25/69	M	70	460	868	778
XPM 39/69	M	65	470	791	687
XPM 29/69	F	18	350	894	830
XPM 19/69	M	60	530	842	713
Average		44	494	688	647
Uganda and Ghana					
808/66	M	48	500	910	990
519/65	F	11	—	680	650
397/68	F	56	290	1 090	1 170
R 271/66	M	34	425	1 095	1 180
R 62/68A	M	28	440	805	875
Average		35	414	916	973

diac muscle whereas the fibers in cases of EMF are 40 per cent larger

The widespread impression that cardiac muscle fibers are hypertrophied is probably due to the fact that there is a much greater variation in cell size in CUO than in EMF Futhermore in CUO the *median* fiber size is larger than the *mean* fiber size—the exact opposite of the findings in EMF

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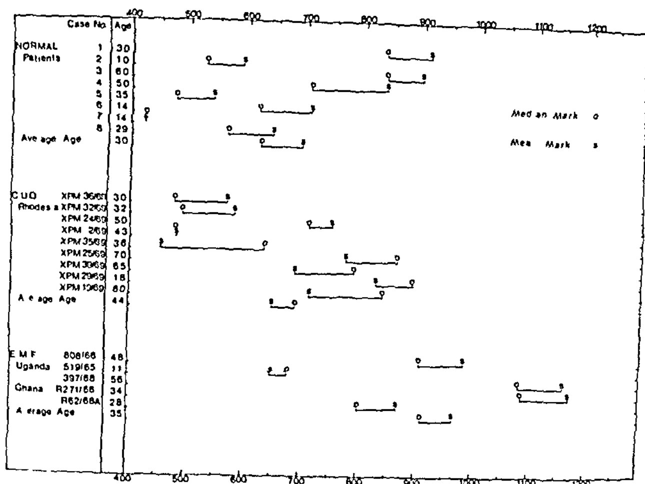


Fig 3 Mean and median muscle widths of cardiac muscle fibers in EMF CUO and normal healthy Africans

Table I Normal African hearts

No	Sex	Age	*Cardiac muscle fiber weight (Gm)*	
			Median	*Mean*
1	M	30	843	920
2	F	10	531	596
3	M	60	842	907
4	M	50	712	842
5	F	35	479	544
6	M	14	622	712
7	M	14	427	427
8	M	29	570	648
Average		30	628	699

obvious that interpretation of a biopsy on the grounds of cardiac muscle fiber size is unsatisfactory and uncertain

Discussion

These results show that the cardiac muscle fibers in CUO are not hypertrophied (which confirms Read s results) whereas in EMF the fibers are hypertrophied, both the mean and median sizes being about 40 *per cent larger than* in CUO or in the controls The explanation for the commonly held belief that hypertrophy is found in CUO and not *in EMF—the complete opposite of* the true findings—is probably as follows In CUO there is a much greater variation in fiber size and there are more interstitial fibers in the myocardium than in EMF which could be misleading if only a cursory examination of the cardiac tissue is made

The reason for the erroneous conclusion that muscle fibers are hypertrophied in CUO may lie in the fact that the *median* value of fiber size is usually so much *larger than the mean* value in any particular case—the direct opposite of the finding in EMF where the *median* value is usually considerably less than the *mean* value (see Fig 3)

The overlap in fiber sizes in CUO and EMF makes it impossible to use cardiac muscle fiber size in *differential diagnosis* of these two diseases

Summary

The average size of the cardiac muscle fibers in cases of CUO is the same as that in normal car

Table II Comparison of cardiac muscle fiber size in CUO and EMF

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Use of lidocaine by continuous infusion

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Steven R Weinstein M D
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Intravenous lidocaine is one of the most commonly used drugs for the management of serious ventricular arrhythmias in the coronary care unit setting The usual method of administration based on the recommendation of Gianelly and associates,[1] is an intravenous bolus of 50 to 100 mg followed by a continuous intravenous infusion of 1 to 4 mg per minute It is a common coronary care unit practice to make frequent changes in the rate of the continuous infusion in response to variations in the frequency of ventricular extrasystoles Rational decisions regarding when and whether to increase or decrease the rate of infusion of the drug within the generally accepted range of safe and effective rates must be based on a knowledge of the plasma half life of continuously infused lidocaine

Considerable disagreement however exists regarding the pharmacokinetics of lidocaine Gianelly and associates[1] based their original recommendations on data indicating that lidocaine administered by continuous infusion without an initial bolus reaches a plateau within 30 to 60 minutes This was later confirmed—even for patients with reduced cardiac output and hepatic perfusion—by another study from the same institution [2] Others [3-5] however primarily by extrapolating from data collected after administration of a single bolus or brief infusion calculated a mean half life of continuously infused lidocaine of almost two hours They implied that a much longer time five to seven hours would be required for steady peak concentrations to be achieved

The present study was designed to resolve the above discrepancy and more clearly define the pharmacokinetics of lidocaine by measuring serial plasma levels of lidocaine during prolonged constant rate infusion

Methods

Seven patients in our cardiac care unit were given lidocaine according to the following regimen A bolus of 1 mg per kilogram was given intravenously while simultaneously an infusion was begun via Harvard pump at a rate of 2 mg per minute for a patient weighing less than 150 pounds 2 5 mg per minute for a weight of 150 to 200 pounds, and 3 0 mg per minute for a weight of over 200 pounds None of our patients was severely ill in shock, or in gross congestive heart failure all had normal liver function tests Three patients were two to seven days after acute myocardial infarction, two patients had mild chronic congestive heart failure and one patient was two days after aortocoronary bypass surgery In all patients plasma lidocaine levels were measured at 0 5 10 20 30 45 60 90 and 120 minutes after the onset of infusion and then hourly for a total of 11 hours * The infusion was then discontinued and blood samples were drawn every 30 minutes for 2 hours

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Milly Factor Clinical Investigator of the Western Cardiac Foundation

Blood samples were kindly analyzed by M B Meyer M D Director of Clinical Pharmacology Astra Laboratories Worcester Mass and by Malcolm Rowland Ph D of the Department of Pharmaceutical Chemistry School of Pharmacy University of California San Francisco

Results

No patient was observed to have achieved steady state blood levels of lidocaine at one hour Fig 1 depicts the time course of mean blood levels in the seven patients After a brief initial peak following bolus administration blood levels fell to 50 per cent of eventual plateau value at 20 minutes Steady state levels did not occur until about 10 hours after onset of infusion although 90 per cent of plateau levels were achieved by about six hours Mean half life based on the decay curves was 90 minutes Peak levels varied from 2 0 to 6 5 μg per milliliter No patient was observed to have central nervous system or cardiovascular signs of lidocaine toxicity In our small group of moderately ill patients without significantly impaired liver function there were no obvious factors correlating with the observed variations in half life plateau time and peak levels

Discussion

Our findings with respect to a prolonged lidocaine infusion are in substantial agreement with the extrapolations from the kinetics of a bolus or brief infusion which suggested a plateau time of five to seven hours [3,5] The practical implications of these findings are as follows

1 If ventricular extrasystoles recur while a lidocaine drip is running and prompt eradication is indicated, a lidocaine bolus should be administered rather than the infusion rate increased The build up time of a lidocaine infusion is too slow to provide the necessary repaid increase in blood levels

2 If an arrhythmia occurs while a lidocaine drip is running at a given rate of infusion the particular rate of infusion should not be considered ineffective (and therefore the rate increased) unless the infusion has been running at that rate for six hours Increasing the rate of infusion before the blood level has approached plateau will frequently result in the use of an unnecessarily high rate of infusion and thus invite an increased incidence of toxicity

3 Extrapolating from the observed drug half life of 1 5 hours a practical method of achieving rapid steady state blood levels of lidocaine without increased risk of toxicity would be to follow the initial bolus with an infusion of double the usual rate for the first hour This method would be of special benefit in the prophylactic use of lidocaine early after acute myocardial infarction During this period the risk of fatal arrhythmias is high and yet since the drug is being employed prophylactically premonitory arrhythmias are not present as a guideline for the achievement of therapeutically adequate blood levels

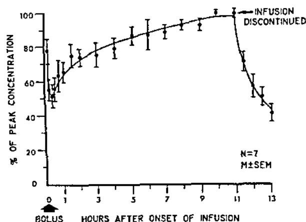


Fig 1 Serial mean plasma lidocaine levels (expressed as per cent of peak level) in seven patients receiving a constant rate infusion of lidocaine preceded by a 1 mg bolus per kilogram of body weight.

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Prinzmetal's variant angina: A clinical and electrocardiographic study

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Since the initial description of atypical ST segment elevations occasionally associated with coronary insufficiency[1] and subsequently the delineation of variant angina pectoris by Prinzmetal and colleagues[2,3] several reports of this syndrome have appeared These have dealt with clinical features[2-6] arrhythmias[2,3,7-10] and coronary arteriography[6,11,12] The varied electrocardiographic picture that can occur in this syndrome is the subject of this report

Materials

Eight patients seen over a period of two years were selected for analysis The only criteria for acceptance was chest pain and electrocardiographic changes during pain characterized by transient ST segment elevation and upright T waves without the appearance of Q waves The patients' ages ranged from 50 to 75 years, five were men and three were women Serum enzymes were evaluated in seven patients Electrocardiograms before and after pain were analyzed for rhythm and contour changes Four patients had cardiac catheterization and three underwent surgical revascularization The electrocardiographic findings were then correlated with the specific anatomic data thus obtained

Case summaries

Patient 1 After experiencing three episodes of pain at rest per day for three weeks unresponsive to nitroglycerin isosorbide dinitrate and propranolol each associated with transient concave ST segment elevations and peaked T waves (Fig 1A) coronary arteriography was performed. The left coronary artery and left ventricular angiogram were normal. The right coronary artery was dominant with 90 per cent narrowing proximal to its bifurcation into the acute marginal and posterior descending arteries The diagnosis of *impending infarction* was made At surgery mechanical endarterectomy and saphenous vein bypass of the right coronary artery were performed. After surgery new Q waves with ST segment elevations and T wave changes were noted in Leads II III and aV_F (Fig 1C) In the eight months since surgery she has continued to experience mild chest pain, now only on moderate exertion

Patient 2 In this woman substernal chest pain at rest had occurred from midnight to 8 A.M intermittently for 3½ years and had become progressively worse in the past 1 month. In addition she experienced six episodes of syncope that were always associated with substernal pain The peripheral pulse at these times was slow and irregular at an average rate of 40 per minute While hospitalized, the electrocardiogram during pain revealed concave ST segment elevation in aV_F and ventricular bigeminy Monitoring also disclosed episodes of repetitive ventricular tachycardia during pain with an average rate of 166 per minute (Fig 2) and Mobitz Type II A V block on one occasion (Fig 3) Neither Q waves nor enzyme elevations occurred at any time during hospitalization Coronary arteriography revealed only mild intimal irregularity of the proximal right coronary artery The left coronary artery and the left ventriculogram were normal After one year the patient has continued to have pain primarily at rest but occasionally with effort despite various combinations of isosorbide dinitrate propranolol and nitroglycerin No syncopal episodes have occurred during this time however she has been maintained on quinidine

Patient 3 This woman with a 3½ year history of chest pain induced by effort was hospitalized with a 4 week history of increasing chest pain occurring at rest and relieved by nitroglycerin. Repeated episodes of pain in the hospital were unresponsive to medical therapy The electrocardiogram consistently demonstrated concave ST segment elevations and blunted T waves and ventricular arrhythmias during pain (Figs 4A and B) The electrocardiogram always reverted to baseline with subsidence of pain No Q waves or serum enzyme elevations occurred Coronary arteriography

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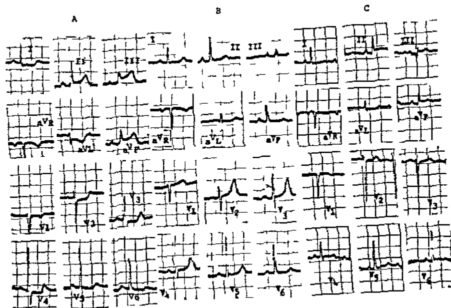


Fig 1 A B and C Patient 1 A Showing concave ST segment elevations during pain. B After pain C Following right coronary artery surgery

revealed a 50 per cent narrowing of the proximal right coronary artery and a 75 per cent occlusion of the posterior descending coronary artery The left ventriculogram was normal. Because of persistence of symptoms saphenous vein bypass surgery to the posterior descending artery was performed. During surgery a plaque was found in the left anterior descending artery and this was also bypassed. Immediately after surgery a left bundle branch block pattern was present (Fig 4C) Because of the recurrence of pain after surgery the patient was restudied with coronary arteriography The bypass to the right coronary artery was completely occluded and the bypass to the left anterior descending artery was partially occluded. Twenty months after surgery she has continued to have chest pain induced by effort with the electrocardiogram showing a persistent left bundle branch block pattern.

Patient 4 This man presented with a one week history of recurrent epigastric and left precordial pain at rest His baseline electrocardiogram revealed symmetrically inverted T waves in V_2 to V_5 without Q waves The serum enzymes were normal. During pain, the electrocardiogram disclosed marked concave ST segment elevations with the T waves now peaked and upright in V_2 to V_6 and at the same time an idioventricular rhythm at 54 per minute was recorded (Fig 5A B, and C) Similar episodes recurred for three successive mornings with the electrocardiograms returning to baseline after each episode A temporary right ventricular pacemaker was inserted to prevent more severe bradyarrhythmias and propranolol was given for the angina Pacing resulted in a left bundle branch block pattern with upright T waves in V_5 and V_6 During an episode of pain, after pacing was instituted, a tall R wave appeared in V_2 through V_4 with concave ST segment elevations and upright T waves Now these changes disappeared within 2 minutes after relief of pain by nitroglycerin (Fig 5) With a combination of permanent ventricular pacing at 68 per minute propranolol and nitroglycerin, the patient has experienced fewer and less severe episodes of pain over the last 5 months

Patient 5 This man was transferred from another hospital with the diagnosis of Prinzmetal's angina The electrocardiogram during all episodes of pain revealed marked concave ST segment elevations and blunted upright T waves in V_2 through V_4 which reverted to baseline immediately after pain This pattern also repeated itself 3 times at rest always from 6 to 8 A.M. without the appearance of Q waves or enzyme elevations While awaiting catheterization he developed another episode of pain not relieved by nitroglycerin as all the prior episodes had been. The electrocardiogram again showed concave ST segment elevations and upright T waves in Leads V_2 through V_4 however a Q wave now appeared in V_3 and the serum enzymes rose No arrhythmias occurred at any time during constant monitoring No further episodes of pain occurred during hospitalization. He has been lost to follow up since discharge

Patient 6 This man presented with crescendo angina The initial electrocardiogram revealed symmetrically inverted T waves in Leads V_2 through V_4 which gave way to marked concave ST segment elevations during pain During one period lasting less than one minute the ST segments were noted to be elevated while the patient was asleep and apparently without pain (Fig 6) These changes receded spontaneously After several days of recurrent pain, there was one severe episode of pain after which the serum enzymes were markedly elevated No Q waves appeared nor did pain recur He has been free of pain in the three months since discharge

Patient 7 This man had effort induced angina for 10 weeks prior to hospitalization and gave a history of transient dizziness associated with the pain usually after the use of nitroglycerin. A treadmill test showed a 2 mm ST segment depression in Lead V_5 (Fig 7) and ventricular tachycardia but no dizziness or syncope At another time while without symptoms nitroglycerin was administered His blood

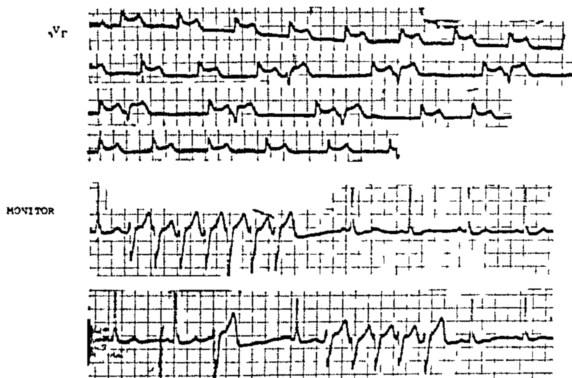


Fig 2 Patient 2 Lead aV$_F$ during pain showing concave ST segment elevations and ventricular bigeminy *Lower panel* monitor lead with repetitive ventricular tachycardia

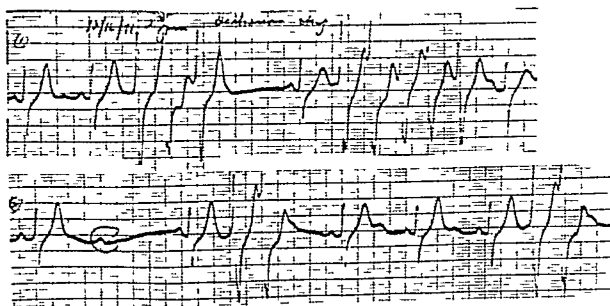


Fig 3 Patient 2 Repetitive ventricular tachycardia and heart block during pain

pressure dropped from 98/70 to 80/50 and a run of ventricular tachycardia appeared associated with dizziness Sinus beats demonstrated concave elevated ST segments simulating a monophasic action potential (Fig 8) These changes subsided in less than two minutes with a return of the monitor pattern to baseline and a marked decrease in ventricular irritability Coronary arteriography revealed a 90 per cent occlusion of the proximal left anterior descending artery the other arteries were normal Saphenous vein bypass was performed and he has been asymptomatic for three months

Patient 8 This man presented with effort angina for six weeks and a positive exercise test Marked concave ST segment elevations appeared in Leads II and III with the onset of pain induced by the exercise test (Fig 9) Leads V_4 and V_5 showed ST segment depressions

Results

Baseline electrocardiogram Normal sinus rhythm was present in four patients Three had a sinus bradycardia of 45 52 and 54 per minute respectively Two patients with bradycardia had rare premature ventricular contractions with a coupling time of 0 60 sec and 0 54 sec respectively

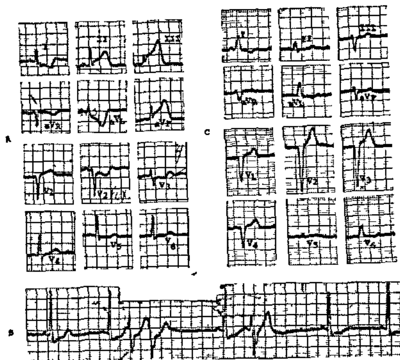


Fig 4 A B and C Patient 3 A During pain, showing ST segment elevations B Ventricular salvos during pain on awakening in morning C After surgery

Two patients had symmetric T wave inversions in the precordial leads and two had diphasic T waves in Leads II III and aV_F. One patient had 0 5 mm J junction depression in V_3 and V_4 as the only abnormality One patient had only 0 5 mm. S T depression in Leads I and aV_L and in the remaining two patients the electrocardiogram was completely normal

The most constant electrocardiographic feature during the pain was the appearance of marked concave ST segment elevations and upright T waves in all eight cases Leads II III and aV_F were involved in three cases Lead III in one case the precordial leads in three cases and a monitor chest lead in the remaining case The T waves were upright in all cases with peaking in three and blunting in others again in the same leads in which the ST segment changes occurred. Reciprocal ST segment depressions occurred in six of eight cases At times the RST T complex took on the appearance of a monophasic action potential In four patients the ST segment elevations during pain occurred in the leads showing the T wave inversions prior to the pain During sleep patient No 6 demonstrated ST segment elevations and peaked T waves unassociated with pain

Electrocardiogram during pain Four out of eight patients demonstrated ventricular arrhythmias during pain Patients No 2 and 7 had ventricular tachycardia at rates of 166 per minute and 187 per minute respectively Patient No 4 demonstrated frequent ventricular premature beats and an idioventricular rhythm at 58 per minute Patient No 3 had runs of ventricular bigeminy and ventricular salvos Mobitz Type II block was noted transiently in patient No 2 A change of QRS morphology occurred in three patients during pain There was a marked increase in height of the R waves in the leads demonstrating the ST T changes which receded after the pain subsided. No Q waves appeared in any of the eight patients during pain

Patient No 4 had a recurrence of pain after pacing was instituted for sinus bradycardia and idioventricular rhythm. The electrocardiogram during pacing showed a left bundle branch block pattern with no R waves in the right precordial leads isoelectric ST segments and upright blunted T waves in V_5 and V_6 During pain while being paced, tall R waves appeared in the left precordial leads with marked concave ST segment elevations in leads V_2 through V_4 (Fig 6) These changes were almost identical as to lead

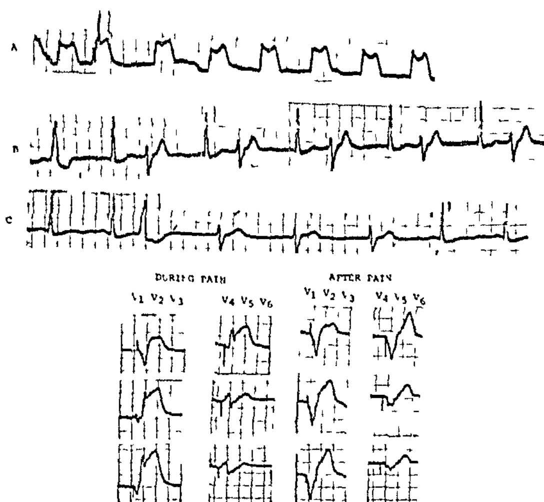


Fig 5 A B and C Patient 4 A ST segment elevation in V_2 during pain B Junctional rhythm and ventricular beats forming bigeminy during pain C Sinus bradycardia fusion beat and escape rhythm at 50 per minute Note that the idioventricular beats are the same as the ectopic beats in B *During pain* after insertion of cardiac pacemaker the ST segments in all precordial leads are more elevated than *after pain*

distribution and pattern when compared with the electrocardiogram during pain before pacing To our knowledge this has not been described previously and suggests that a diagnosis of variant angina is possible even in the presence of a pacemaker rhythm

Serial ECG s All patients except patient No 7 repeated their abnormal patterns on several occasions In Cases 5 and 6 new Q waves subsequently developed in the leads reflecting the variant changes These patients have been asymptomatic since Patients No 2 and 4 have had stable electrocardiograms without evidence of transmural infarction The electrocardiogram of patient No 1 showed a Q wave after saphenous vein bypass surgery and subsequently revealed serial changes typical of an acute inferior wall myocardial infarction The post saphenous vein bypass tracing showed a left bundle branch block pattern in patient No 3

Anatomic correlation Four patients had cardiac catheterization permitting localization of the coronary artery lesions Patients No 1 and 3 whose changes were in the right coronary arteries demonstrated inferior lead changes However patient No 2 who also had inferior lead changes had no significant right coronary artery disease Correlation in patient No 7 was not possible since the electrocardiographic findings were obtained only in one lead during monitoring for arrhythmia demonstrating the need for a 12 lead electrocardiogram during these episodes

Discussion

The clinical picture of variant angina described by Prinzmetal and co workers[2,3] was found in seven of our patients However, variability is demonstrated by three patients who had pain on effort as well as at rest, and in one who had only effort induced angina Only four out of seven patients treated with nitroglycerin obtained relief

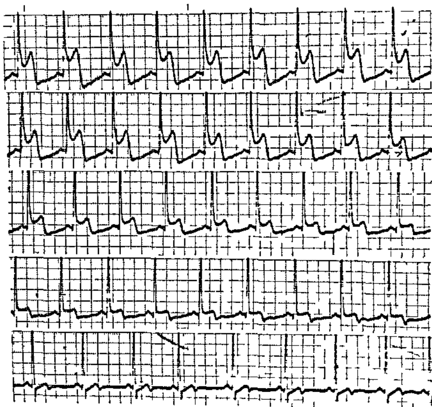


Fig 6 Patient 6 Monitor lead recorded during sleep and without pain The entire episode lasted less than one minute The top 4 panels are continuous

ST segment elevations The electrocardiogram provides the key to diagnosis In all patients concave ST segment elevations occurred during pain and disappeared after its subsidence or after infarction The findings in one patient of concave ST segment elevations during pain in the presence of a left bundle branch block pattern during right ventricular pacing has not been described previously The findings in one patient of concave ST segment elevations during sleep has been previously described[13] and no consistent relation to rapid eye movement sleep could be demonstrated[14] This change during sleep has also been described by Guazzi and associates[13] and suggests that a diagnosis of variant angina really rests on the electrocardiogram not on the description of the pain[13] Fortuin and Friesinger[15] and Bobba and colleagues[16] have emphasized the diagnostic importance of ST segment elevations recorded during an exercise test as illustrated by patient No 8 The localization of the ST segment elevation to Lead III confirms the importance of multiple lead recording during stress testing If only V_5 was examined this would appear like a routine positive stress test documented by ST segment depressions

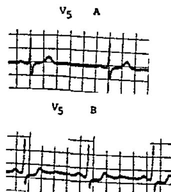


Fig 7 A and B Patient 7 A V_5 before exercise B V_5 three minutes after exercise

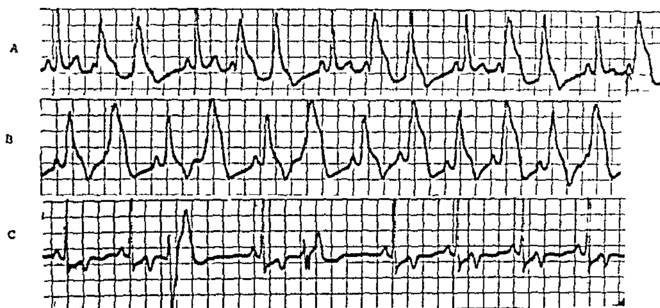


Fig 8 A B and C Patient 7 A and B *Monitor* lead after nitroglycerin showing frequent PVC s and salvos C Two minutes after nitroglycerin showing less frequent multifocal PVC s

Table I Summary of eight cases

Patient	*Age (yr)*	*Sex*	*Pain*		*B P*	*Murmur*	*Relief with nitro*	*Baseline ECG*			*ECG during pain*	*Arrhythmias*
			*R**	*F*				*SB*	*ST depression*	*T*		
1	60	F	+	—	175/85	ASM	—	—	—	D_2 D_3 aV_F	C ST and P T 2 3 aV_F R ST 1 aV_L V_2 V_4	
2	47	F	+	—	—	—	—	—	—	D_2 D_3 aV_F	C ST and P T 2 3 aV_F R ST in I aV_L	VPB s VT Ht block
3	52	F	+	+	150/70	ASM EDM	+	52	0 5 in 1 aV_L	—	C ST and B T 2 3 aV_F R ST 1 aV_L V_2 V_3	V bigeminy + salvos
4	75	M	+	—	170/100	ASM	±	45	V_1 V_3	I V_1 V_3	Tall R V_2 V_4 C ST and P T V_2 V_6	Idioventricular 54/min.
5	57	M	+	—	—	S_4	+	—	—	—	Tall R V_2 C ST and B T V_2 V_4	—
6	69	M	+	+	170/90	S_4	—	—	—	I 1 aV_L V V_5	C ST and P T V_2 V_4	—
7	50	M	+	+	—	—	—	58	V_3 V_5	—	C ST monitor	VT
8	68	M	—	+	170/84	ASM	Not tried	—	—	—	C ST III R ST V_3 V_5	—

Abbreviations R = rest E = effort + = present — = normal or absent ASM = apical systolic murmur EDM = early diastolic murmur SB = sinus bradycardia VPB = ventricular premature beat VT = ventricular tachycardia C ST = concave ST segment elevation, R ST = reciprocal ST depression D = diphasic B T = blunt T wave P T = peaked T wave I = inverted T wave

Cardiac arrhythmias The frequency and seriousness of arrhythmias in this syndrome is well documented and demonstrated by the ventricular arrhythmias in three patients and transient heart block in one patient The peculiar findings of concave ST segment elevation and ventricular tachycardia after nitroglycerin has not been described previously (see below)

The mechanism of the arrhythmias is uncertain Presumably this is related to ischemia[17]

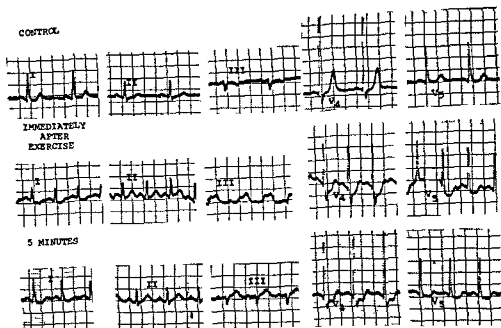


Fig 9 Patient 8 *Upper panel,* Pre exercise tracing *Middle panel* Immediately post exercise *Lower panel,* Five minutes post exercise

resulting in either an ectopic focus or re entry It is unclear why some patients develop them and others do not Note however that the finding of normal coronary arteries in this syndrome is no protection against ventricular arrhythmias and/ or syncope (patient No 2) In fact Cheng and co workers[18] have described a patient with variant angina who died in ventricular fibrillation Thus as recently described a normal coronary ar teriogram does not necessarily indicate a benign course [18] in contrast to Bemiller and associates [19] recent findings in classic angina

Pathophysiology In their report of 1960 Prinzmetal and colleagues[3] theorized that a difference in electrolyte shifts explained why the ST segments were depressed in the usual form of angina and elevated in variant angina They pro posed that ST segment depression was associated with an increase in intracellular K^+ and a decrease in intracellular Na whereas ST seg ment elevation resulted from the reverse There is however no confirmation of this theory Parker and associates[20] in fact found that ischemia with ST segment depression is associ ated with extracellular leakage of K^+ a discovery which makes the hypothesis of Prinzmetal and co workers doubtful

At a macroscopic level Bayley and LaDue[21] in their work with dogs provided a model which may explain the basis of the electrocardiograph ic findings They progressively decreased the luminal diameter of the coronary artery which initially resulted in symmetric T wave inversion If the lumen was further constricted the ST seg ment became elevated with the T waves now upright and peaked. Release of the ligature resulted in reversion to the control appearance within minutes They also noted that ischemic T waves could persist for long periods without progression

The similarity between results cited in this paper and those of Bayley and LaDue s experi ments is obvious Presumably occlusion of a ma jor coronary artery resulted in marked ischemia sufficient to progress to variant ST T changes but not to frank infarction Patient No 6 clearly demonstrates how a stable ischemic pattern can persist With recurring ischemia the inverted T waves gave way to markedly elevated ST T changes and with subsidence of pain reverted to the original pattern However after a severe pro longed episode clinically distinguishable infarc tion occurred and the abnormal R ST changes persisted that is reversion to baseline after sub sidence of pain did not occur This would suggest according to Bayley and LaDue s model that the ischemia was prolonged beyond the time when recovery could occur

The mechanism of the tall R wave has been postulated to be a transient conduction disturbance [2] Bayley and LaDue also noted it in dogs However, further work must be done to elucidate the basis of the R wave changes

Patient No 7 provides an unusual opportunity to surmise on pathophysiology His variant changes appeared only after nitroglycerin was given sublingually and were associated with the recurrence of his dizziness as well as with a significant drop in blood pressure A treadmill test which resulted in pain and ventricular tachycardia gave rise to 2 mm ST segment depression not to elevation Guazzi and colleagues [2] while monitoring patients with variant angina found that the ST segment elevations coincided with a drop in blood pressure and generally preceded the pain In some cases the ST segment elevations occurred in the absence of pain The observation may suggest a transient neurohumoral change underlying the whole process It would also explain why variant angina may occur in the presence of normal coronary arteries The difficulty still remains however of identifying this mechanism and of discovering how it might induce coronary spasm [12 23] A catecholamine effect would seem unlikely since the coronary arteries have beta receptors which would result in dilation The lack of consistent beneficial results with propranolol therapy also mitigates against this hypothesis

The strikingly abnormal electrocardiographic changes with pain at first glance would suggest infarction Yet within minutes after subsidence of pain they disappear The hope would be to predict who would infarct and perhaps intervene surgically, however this is made difficult by the absence of any distinguishing features indicating impending infarction and the absence of a remediable lesion in some cases Perplexing are the poor results in two of three patients who underwent surgery

Thus we are left with a syndrome the only constant feature of which is the electrocardiogram Whether it encompasses one or more entities and what the basic pathophysiology underlying these electrocardiographic changes is must await further work

Summary

Eight patients with 'variant' angina pectoris were analyzed for electrocardiographic features before during and after chest pain All patients showed marked concave ST segment elevations with upright T waves during pain which disappeared with subsidence of pain Ventricular dysrhythmias were noted in four patients Three had ventricular tachycardia and one had an idio ventricular rhythm In addition one patient had a transient Mobitz II atrioventricular block The electrocardiogram during pain at the time of right ventricular pacing in one patient revealed elevated ST segments with upright T waves in the previously involved leads Coronary arteriography in four patients revealed an isolated single lesion in three and normal coronary vessels in the other The possible basis of the electrocardiographic findings is discussed

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The significance of right aortic arch in D-transposition of the great arteries

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The detection of a right aortic arch on the plain chest x ray of a patient suspected of having cardiac disease has both diagnostic and therapeutic implications [1] The prevalence and importance of a right arch in patients with tetralogy of Fallot and truncus arteriosus has been widely commented upon The incidence of right arch in d transposition of the great arteries (d TGA), however has been variously quoted as between 4 and 75 per cent [2,3] Pediatric cardiology textbooks[4,5] state that the incidence of right arch in d TGA is low but they provide no further documentation The purpose of our study was to determine the incidence of right arch in d TGA and its significance

Materials and methods

The population studied consisted of 195 consecutive cases of d TGA catheterized from 1965 to early 1972 at The Children's Hospital Medical Center Boston (CHMC) In most cases the diagnosis of a right arch was based on careful review of the plain chest x rays When the side of the arch could not be determined on chest x rays the biplane angiograms were reviewed The arch was considered to be right sided if it arched over the right main stem bronchus to the right of the trachea, and left when it arched over the left main stem bronchus to the left of the trachea. In some cases the right lateral view was helpful the trachea bowed anteriorly when the aortic arch was right sided and it then passed immediately behind the esophagus to descend on the left, while the trachea was straight in lateral view in cases of left aortic arch Catheterization reports and data were reviewed in all patients

The cases were divided into groups depending on the presence or absence of a ventricular septal defect, significant pulmonary stenosis and associated cardiac malformations. The diagnosis of pulmonary stenosis (PS) was based on at least two of the following criteria (1) a pressure gradient across the left ventricular outflow tract greater than 30 mm Hg (2) angiographic evidence of severe PS (3) hypoxic patients requiring a systemic to pulmonary anastomosis

In order to compare the prevalence of right aortic arch in other cardiovascular lesions at our institution we reviewed the angiographic diagnostic file on 102 consecutive patients with tetralogy of Fallot (1969 to 1971) 102 patients with valvar PS (1967 to 1971) and 91 patients with ventricular septal defect (1969 to 1971) Fifty six consecutive cases of truncus arteriosus and 57 cases of heterotaxy syndrome were also reviewed These were collected from the angiographic and autopsy files Statistical analysis was performed using the chi square test in two by two table

Results

Right aortic arch was present in 16 of 195 patients with d TGA an incidence of 8 per cent (Table I) The lowest frequency was in patients with d TGA and intact ventricular septum (4 per cent)

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Table I Incidence of right aortic arch in 195 patients with d transposition of great arteries (d TGA)

	Number	*Right aortic arch*	*Percentage*
d TGA (total)	195	16	8%
IVS (total)	75	3	4%
with P S	4	0	0%
without P.S	71	3	4%
VSD (total)	120	13	11%
with P.S	38	6	16%
without P S	82	7	9%

Abb evi tions IVS = intact ventricular septum PS = pulmonary stenosis VSD = v ntricular septal d fect.

Table II Associated complex cardiac malformations in patients with d TGA according to the site of aortic arch

	Total no	*No with severe malformations*	*Percentage*
LEFT ARCH			
IVS (with or without PS)	72	3	4%
VSD (with or without PS)	107	36	34%
Total	179	39	22%
RIGHT ARCH			
IVS (with or without PS)	3	1	33%
VSD (with or without PS)	13	7	54%
Total	16	8	50%

Abb evi t s a in T ble I

and highest in those with VSD and PS (16 per cent) In the presence of VSD without PS a right aortic arch occurred in 11 per cent of the pa tients

An associated cardiac malformation occurred in 22 per cent of the patients with transposition VSD (with and without PS) and a left aortic arch

When a right arch was present with transposi tion 50 per cent of the patients had an associated complex cardiovascular lesion (Table II) The spe cific complex malformation and their incidences are outlined in Table III Coarctation arch inter ruption and atrioventricular valve anomalies did not occur in the right aortic arch group

In heterotaxy the incidence of right aortic arch was 44 per cent irrespective of cardiac position (e g dextrocardia or levocardia) In 33 autopsied patients where spleen pathology was definitely known a right arch seemed to be very common in the asplenia group (76 per cent) and less com mon in the polysplenia group (25 per cent p value = 0 01) Among the cases with heterotaxy in whom the position and the absence of the hepatic segment of inferior vena cava (IVC) could be ascertained by catheterization or autopsy it was noted that the absence of the IVC was com monly associated with a left arch (10 of 12 cases, or 80 per cent) and a right arch was commonly found in cases with left IVC (14 of 21 cases or 61 per cent)

Discussion

The incidence of right aortic arch in a general population without congenital heart disease was reported to be 0 1 per cent [6] From our study it ap pears that the incidence of right arch in patients with d TGA (8 per cent) is significantly higher than in the normal population but not as prev alent as in patients with tetralogy of Fallot (24 per cent) or with truncus arteriosus (38 per cent) Among the patients with d TGA the incidence seems highest in those with VSD and PS and

Table III Specific cardiac malformations associated with dextro transposition of the great arteries

Malformation	Left arch		Right arch		Total	
	No	Per cent	No	Per cent	No	Per cent
Total number	39	22	8	50	47	24
Arch anomalies (coarctation or interruption)	14	8	0	0	14	7
Single ventricle	10	6	1	6	11	6
Mitral valve disease	8	5	0	0	8	4
Juxtaposition of atrial appendages	6	3	2	13	8	4
Hypoplastic right ventricle	5	3	0	0	5	3
Heterotaxy	1	0 6	5	31	6	3
Tricuspid atresia	4	2	0	0	4	2
Cor triatriatum	1	0 6	0	0	1	0 5

Table IVA Incidence of right aortic arch in other cardiac malformations

Cardiac malformation	Total no	Right arch		Left arch		Double arch	
		No	Per cent	No	Per cent	No	Per cent
Tetralogy of Fallot	102	24	24	76	74	2	2
Ventricular septal defect	91	2	2	88	97	1	1
Pulmonic stenosis	102	0	0	102	100	0	0
Truncus arteriosus	56	21	38	31	55	4	7
Heterotaxy syndrome	58	25	43	32	55	1	2

lowest in patients with an intact ventricular septum In d TGA a right arch was associated with other complicated cardiac malformations in 50 per cent of the patients as compared to 22 per cent in those with a left arch Heterotaxy syndrome was the most common abnormality seen (31 per cent) in patients with d TGA and a right arch

Why a right arch is more common in patients with cono truncal malformation (e g d TGA, tetralogy of Fallot, truncus arteriosus) is unclear It is interesting to note that birds and reptiles usually have a right arch whereas in mammals a left arch is common Van Praagh and associates[7] consider blood flow to be critical in the development of the arch in the cono truncal malformations associated with a right arch the flow through the aorta is increased—e g tetralogy of Fallot or d TGA with PS If one considers the direction of blood flow the right ventricular flow vector is directed superiorly leftward and posteriorly and the left ventricular flow vector is directed superiorly anteriorly and rightward Now if pulmonary outflow is obstructed (e g, as in tetralogy) there would be a reduction in right ventricular flow vector and a relative augmentation of the left ventricular flow vector which is directed rightward superiorly, and somewhat anteriorly towards the right dorsal aorta Since flow is at least one factor controlling the persistence or involution of vascular structures both arterial and venous, then the reduction of the right ventricular flow vector with absolute or relative augmentation of the left ventricular flow vector would theoretically at least, predispose towards the development of a right aortic arch However this does not explain why the majority of cases of tetralogy of Fallot do not have a right arch

It is likely therefore that factors other than

Table IVB Incidence of right aortic arch with heterotaxy syndrome and in relation to spleen pathology and heart position

	Total	Right arch	Percentage	Left arch	Percentage
HETEROTAXY SYNDROME					
Right IVC	14	8	59%	6	41%
Left IVC	21	14	70%	7	30%
Absent hepatic segment of IVC	12	2	17%	10	83%
SPLEEN PATHOLOGY					
Asplenia	21	16	76%	5	24%
Polysplenia	12	3	25%	9	75%
HEART POSITION					
Dextrocardia	21	11	52%	10	48%
Levocardia	36	17	47%	19	53%

hemodynamics are important in determining the location of the arch Furthermore D Cruz and colleagues[6] have pointed out that the arch is developed before the completion of cono truncal development and suggested that the blood flow does not play a critical role in determining the site of the arch

According to Congdon and Wang[8,9] whether one has a left or right aortic arch has nothing whatever to do with whether the left fourth or the right fourth aortic arch persists Both the left and right fourth arches normally persist Which aortic arch persists as the definitive one depends rather on which dorsal aorta undergoes involution Normally it is the right dorsal aorta that undergoes involution immediately distal to the seventh intersegmental artery (the embryonic subclavian artery)

Among the patients with heterotaxy syndrome we found that the position of the heart (dextrocardia or levocardia) was not related to the site of the arch The incidences of right and left arch were almost equal when the inferior vena cava (IVC) was on the right whereas a right arch was more common when the IVC was on the left (70 per cent) The absence of the hepatic segment of the IVC was associated with a left arch in over 80 per cent of the cases

Summary

A review of 195 cases of d TGA disclosed the incidence of right aortic arch to be 8 per cent In cases associated with VSD and PS the incidence was higher (16 per cent) Fifty per cent of the cases with right arch had other severe cardiac malformation

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Cardiac dysfunction in unselected chronic alcoholic patients
Noninvasive screening by systolic time intervals

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Boston Mass

Myocardial depression has been demonstrated in chronic alcoholic patients deliberately selected by exclusion of other illness [1] Since there are no such studies in unselected chronic alcoholic patients we investigated 60 such patients consecutively admitted to a detoxification unit

Subjects and methods

Systolic time intervals were recorded in 60 ambulatory unselected male chronic alcoholic patients admitted to a detoxification unit (mean age 41 years) All were examined 48 to 72 hours after their last alcohol consumption All subjects had in common a long history of excessive alcohol intake Even though none required hospitalization 52 of them had one or more signs or symptoms of one or more disorders permitting subdivision into four main groups by organ system cardiovascular (31 patients) pulmonary (29 patients) gastrointestinal (24 patients) and neurological (21 patients) Eight were clinically free of disease

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Polygraphic recordings were performed with subjects recumbent in the postabsorptive state and during expiratory apnea Recordings were made with a Physioscript 312 polygraph (F Schwarzer GMBH, Munchen) including Lead II of the ECG, phonocardiogram at the mesoapex, and carotid pulse (time constant 3 2 seconds)

Measurements Measurements in five consecutive beats were averaged Heart rate (HR) was obtained from the cycle length (R R interval of the ECG) Zero time was the initiation of the QRS complex (q) Other time measurements were made from q The carotid upstroke (q CAR_u) nadir of the carotid incisura (q CAR_{In}) and the onset of the aortic component of the second heart sound (q II_A)

Calculations As described elsewhere [2] electromechanical systole (EMS) was calculated as (q II_A) left ventricular ejection time (LVET) is (q CAR_{In}) *minus* (q CAR) and pre ejection period as EMS *minus* LVET The ratio PEP/LVET was obtained Means were calculated for the group as a whole and for the four subgroups comprising patients with evidence of abnormalities in various organ systems Rate correction Regression equations were used to correct the LVET and EMS as previously reported [3] using the appropriate slope constants to yield the ejection time index (ETI) and electromechanical systole index (EMSI)

Results

The results are summarized in Table I The mean pre ejection period (PEP) was normal although the scatter (SD) was greater when com

Table I Clinical data in 60 ambulatory male chronic alcoholic patients*

	Total group	Subgroups			
		Cardiovascular	Pulmonary	G I	Neurological
N	60	31	29	24	21
Age					
Mean	41 0	41 9	40 8	44 2	41 1
SD ±	9 6	10 7	9 3	10 0	9 5
SE ±	1 2	1 9	1 7	2 0	2 1
Heart rate					
Mean	82 8	80 6	84 7	90 0	75 0
SD ±	17 7	17 9	19 8	11 3	13 2
SE ±	2 3	3.2	3 6	2 3	2 9
EMS					
Mean	343 8	354 0	343 [illegible]	3[illegible]6 2	351 0
SD ±	34 9	34 6	40 6	33 4	37 6
SE ±	4 5	6 2	7 6	4 9	8 2
EMSI					
Mean	500 0	504 8	499 3	500 0	[illegible]04 1
SD ±	20.3	19 4	17 4	23 0	23 1
SE ±	2 6	3 4	3 2	4 8	5 0
PEP					
Mean	99 3	100 3	96 0	100 0	102 9
SD ±	20 5	21 9	19 4	23 7	24 7
SE ±	2 6	3 9	3 6	[illegible] 7	5 6
LVET					
Mean	245 5	252 5	242 0	232 0	252 7
SD ±	33 2	35 6	34 8	25 1	30 5
SE ±	4 3	6 4	6 5	5 1	6 7
ETI					
Mean	349 0	362 2	357 3	344 6	364 0
SD ±	17 7	39 5	41 2	14 9	46 6
SE ±	2 3	7 2	7 7	3 1	10 4
PEP/LVET× 10^2					
Mean	41 6	41 1	40 5	45 1	41 8
SD ±	11 9	13 0	11 2	12 3	13 4
SE ±	1 5	2 3	2 0	2 5	2 9

*t test not applicable because of subjects appearing in more than one subgroup

pared to previously reported results[1] both in the alcoholic group as a whole and when separated into four subgroups The values for LVET ETI EMS and EMSI were comparable to the values reported by this laboratory in clinically healthy chronic alcoholic patients[1] When the group was subgrouped according to evidence for other diseases the means for age EMS EMSI PEP and PEP/LVET were approximately the same as for the entire series (Table 1)

Discussion

Abnormal cardiac performance has been clearly demonstrated in clinically healthy alcoholic patients when evaluated both by invasive[4] and by noninvasive[1] methods Our unselected alcoholic patients were subdivided into groups having symptoms and signs in the cardiovascular pulmonary, gastrointestinal and neurologic systems Heart rate was significantly higher for the group and each subgroup when compared to previously reported normal control subjects and was quite similar to the values reported by us in otherwise healthy alcoholic subjects[1] We have no evidence that relative tachycardia may be associated with a specific mechanism It may be compensatory—i.e. to maintain cardiac minute output in the presence

Cardiac dysfunction in unselected chronic alcoholic patients
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Experimental and laboratory reports

Propranolol vs saphenous vein graft bypass for impending infarction (preinfarction syndrome)

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The treatment of impending infarction has always presented a great challenge to the physician and evaluation of a specific drug or other mode of therapy is difficult for two reasons First, the outcome of impending infarction has been in the past probably more uncertain than in other phases of coronary disease One can only conjecture concerning the pathophysiology of this stage of the disease probably the mechanism is variable ranging from fresh change in an artery causing progressive narrowing to impaired or diminished blood flow secondary perhaps to discharge of catecholamines into the blood stream with coronary vasoconstriction Second, the term impending infarct is employed in different ways by physicians both cardiologists and cardiac surgeons Thus synonyms found in the literature include (1) acute coronary insufficiency (2) intermediate syndrome (3) unstable angina (4) progressive angina (5) crescendo angina (6) angina decubitus and (7) myocardial ischemia—severe [1,3]

Patients have been included who experienced one or possibly two episodes of severe prolonged anginal pain but without Q waves or ST elevation in the ECG or enzyme changes significant of major infarction We believe that such attacks indicate subendocardial necrosis therefore we have restricted impending infarction to two distinct types of patient[4,5] (1) those without previous angina who suddenly begin to experience repeated chest pain, even at rest and at night and (2) more commonly those with previous angina of effort who suddenly develop a distinct change in symptoms in that the pain occurs much more frequently and severely without or with less effort. Nitroglycerin may lose its effect or a larger dose may be required

In impending infarction the ECG may remain normal or unchanged but usually shows fresh ST depressions and/or T inversion Similarly the enzyme values may be normal or slightly elevated. In our experience the course of impending infarction has been variable but generally favorable [4,5] In over three fourths of patients the crescendo anginal pain has gradually subsided after two to four weeks occasionally it has lasted over a period of six to eight weeks Less than 10 per cent of patients developed transmural infarction from which most recovered and 20 per cent went on to subendocardial necrosis the mortality rate has been less than 4 per cent for all patients [4,5] although higher figures have been reported [6]

In the 1950 s and early 1960 s a number of articles appeared purporting to show that anticoagulant therapy improved the prognosis in impending infarction A review of these studies made it clear that the number of cases in each was small the various types of cases were included and that controls were absent or inadequate On the other hand in a large controlled series of 172 cases the senior author (A M M) found no significant difference between those receiving anticoagulant drugs and those treated only with rest sedation and if necessary a nar

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of reduced stroke volume Indirect evidence for this is provided by the consistently abnormal ejection time

LVET corrected for heart rate (ETI) is depressed in 'healthy alcoholic patients[1] We found that it was depressed in the present group Stroke volume is the principal factor that influences ejection time Low ejection time index is most consistent with diminution in stroke volume[2,5] The ratio PEP/LVET when abnormally increased is characteristic of failing cardiac performance We found the ratio PEP/LVET elevated owing to the low ejection time

Although the scatter (SD) was greater the mean value obtained in this study for PEP is quite similar to that previously reported by us in a normal control group[1] We have no explanation for the normal mean value (99 msec for the entire group) and particularly for the similar value in the 31 patients with cardiovascular signs or symptoms However, the "normal alcoholic group had a mean of 107 msec.[1] The difference of 8 msec was statistically different, but one might question its biologic significance In any case, the results indicate that the abnormally low ETI and increased PEP/LVET in the clinically normal alcoholic patients and in this large unselected group might be ascribed to the factor common to both alcohol

Summary

Chronic alcoholism produces abnormal cardiac function even in asymptomatic patients free of other disease Sixty unselected chronic alcoholics 52 of whom proved to have symptoms and signs consistent with various disorders (cardiovascular, pulmonary gastrointestinal and neurologic) were evaluated by systolic time intervals Both the group as a whole and separately when subgrouped by associated diseases showed evidence of cardiac malfunction on the basis of decreased left ventricular ejection time and abnormally increased ratio of pre ejection time to ejection time

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Experimental and laboratory reports

Propranolol vs saphenous vein graft bypass for impending infarction (preinfarction syndrome)

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The treatment of impending infarction has always presented a great challenge to the physician and evaluation of a specific drug or other mode of therapy is difficult for two reasons First, the outcome of impending infarction has been in the past probably more uncertain than in other phases of coronary disease One can only conjecture concerning the pathophysiology of this stage of the disease probably the mechanism is variable ranging from fresh change in an artery causing progressive narrowing to impaired or diminished blood flow secondary perhaps to discharge of catecholamines into the blood stream with coronary vasoconstriction Second the term impending infarct is employed in different ways by physicians both cardiologists and cardiac surgeons Thus synonyms found in the literature include (1) acute coronary insufficiency (2) intermediate syndrome (3) unstable angina (4) progressive angina (5) crescendo angina (6) angina decubitus and (7) myocardial ischemia—severe[1,3]

Patients have been included who experienced one or possibly two episodes of severe prolonged anginal pain but without Q waves or ST elevation in the ECG or enzyme changes significant of major infarction We believe that such attacks indicate subendocardial necrosis therefore we have restricted impending infarction to two distinct types of patient[4,5] (1) those without previous angina who suddenly begin to experience repeated chest pain even at rest and at night and (2) more commonly those with previous angina of effort who suddenly develop a distinct change in symptoms in that the pain occurs much more frequently and severely without or with less effort. Nitroglycerin may lose its effect or a larger dose may be required

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Summary

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Table II ECG in impending infarction

Patient no and initials	Control ECG	Impending phase	Result
1 E B	LVS pattern	More ST	Sub Isch
2 G B	LVS pattern	More ST	Sub Isch.
3 M C	Auricular fibrillation	Dramatic ST and Ti s	Sub Inf †
4 J D	Q III aV_F	Dramatic ST	Sub Inf
5 J F	Negative	ST V_5 V_6	No complication
6 V G	Negative	ST V_3 V_5	Sub Isch.
7 J G	LBBB Q s Ti s	More ST and Ti s	Sub Isch
8 I G	LVS pattern	Dramatic ST and Ti s	Sub Inf
9 M H	Slight ST V_5 V_6	More ST V_4 V_6	Sub Inf
10 S K	Slight ST II III aV_F	More ST also V_4 V_6	Sub Isch.
11 L K	Slight ST V_4 V_6	Dramatic ST I II aV_L, aV_F V_1 V_6	Sub Inf
12 I L	Negative	Slight ST V_4	Sub Isch.
13 W R	Negative	Ti V_1 V_4	No complication
14 J R	Negative	ST V_4	Sub Isch.
15 J S	ST I II aV_F V_4 V_6	More ST V_4 V_6 and Ti s	No complication
16 R S	ST II III aV_F	More ST I aV_F	No complication
17 J S	LBBB Q s Ti s	More ST I aV_L	No complication
18 M V	ST and Ti s	More ST and Ti s	Sub. Isch.

Subendocardial ischemia
†Subendocardial infarction

patient had had a pre existing anginal syndrome five had had attacks of subendocardial infarction and in five transmural infarction had occurred previously

The ECG findings are shown in Table II It will be seen that the original ECG was normal in five patients In all the others the ECG had been abnormal but stable for months prior to the stage of impending infarction Digitalis had not been used or had been discontinued for at least three weeks

Results

During the period of observation under treatment with propranolol not a single death occurred in this series Furthermore there was no instance of transmural infarction as evidenced by the appearance of ST elevation and/or Q waves The ECG showed new or further ST depression and/or T wave inversion in every case (Fig 1) but in only five did these persist beyond seven days, long enough to diagnose subendocardial infarction (Cases 3 4 8 9 and 11) Only one of these five patients with subendocardial infarction had to be hospitalized because as stated above one episode of pain was severe and lasted 30 minutes. The ECG showed definite depression and T wave inversion (Fig 2) His temperature was 100 to 101° F for five days and the serum glutamic oxaloacetic transaminase rose to 136 the lactic dehydrogenase to 980 and the creatine phosphokinase activity to 169 These figures quickly reverted to normal and the patient made a good recovery In the remaining 13 cases the ST and T changes lasted less than seven days indicating subendocardial ischemia It is likely that no significant fresh anatomical change occurred in the heart in these cases particularly in five of them in which the alteration in the ECG was very slight and fleeting

It is noteworthy that in the present series of cases the average duration of impending infarction following the use of propranolol was shortened to eight days Only four cases lasted over 10 days and seven patients complained of pain less than five days (Table I)

Discussion

Our results emphasize the danger of drawing conclusions from a small number of cases in evaluating therapy surgical or medical in any phase of coronary disease It is tempting to attribute our zero mortality rate and absence of transmural infarction in the present 18 cases of impending infarction and several others treated later to the use of propranolol but study of a

Table I Propranolol dosage in impending infarction

Patient no and initials	Age (yr)	Sex	Duration after propranolol (days)	Previous diagnoses (MI)*				Propranolol (mg)
				AP	CI	CO	Hyp	
1 E B	72	F	4	X	X		X	160
2 G B	73	F	5	X	X		X	320
3 M C	75	M	27	X				160
4 J D	52	M	18	X		X	X	160
5 J F	62	M	4	X				40
6 Y G	65	F	7	X				30
7 J G	80	M	14	X		X		160
8 I G	61	M	14	X			X	320
9 M H	60	M	21	X	X			160
10 S K	53	M	6	X				40
11 L K	56	F	9	X			X	120
12 I L	54	M	6	X				160
13 W R	69	M	4	X	X	X		80
14 J R	61	M	7	X			X	160
15 J S	70	M	3	X		X		240
16 R S	70	F	8	X	X			130
17 J S	79	M	7	X	X	X	X	160
18 M V	48	M	5	X				40

Abbreviations MI = myocardial infarction AP = angina pectoris CI = coronary insufficiency CO = coronary occlusion Hyp = hypertension.

cotic for a short time [4,5] Actually the controls appeared to fare slightly better

A new phase in the treatment of coronary disease with anginal pain began with the introduction of saphenous vein aortocoronary bypass which, in a short time has been accepted enthusiastically by most cardiac surgeons and some cardiologists [7-13] However, in view of the natural course of coronary disease, the inadequate period in which the operation has been performed and the absence of controlled studies many cardiologists remain unconvinced of the value of the procedure other than to relieve angina for a shorter or longer period [14-20] Yet it is not surprising that those particularly surgeons who consider the bypass procedure effective in increasing coronary flow beyond the area of obstruction in angina pectoris would extend its application to the stage of impending infarction, or even acute infarction with shock in which the need for more blood flow is immediate In impending infarction it is assumed that major infarction will be prevented During the past year or two there have been reports of favorable results following operation in a number of small series of cases of impending infarction as defined by us *[2,21-29] The number of patients in each series has varied from 3 to 14 Of 40 patients reported operated on two died the remainder tolerated the procedure well and the anginal pain subsided without evidence of significant infarction *One* author has stated that the acute pre infarction syndrome, when associated with critical coronary artery lesions particularly in the absence of collaterals represents the leading indication for saphenous vein bypass surgery' [24]

Material

In 1970 71 the senior author had occasion to treat 18 successive patients with impending infarction with propranolol, in addition to rest The dose varied from *30 to 320 mg* daily (Table I) The usual amount was 160 mg All the patients were treated at home except one who experienced pain for 30 minutes The duration of the new symptoms of impending infarction prior to treatment varied from one to several days Every

*A series of 41 patients has been reported,[30] but it is our impression that included are cases which do not conform to our definition of impending infarction

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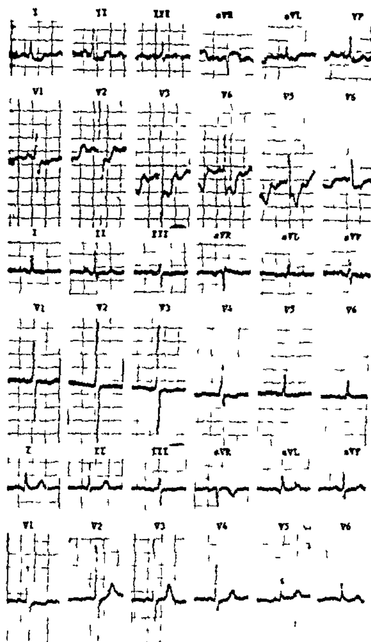


Fig 1 A through C L K a 56 year old woman with angina pectoris A (6/28/1970) shows dramatic ST and T changes B (7/6/1970) shows impending infarction Changes are much less C (7/11/1970) is normal

large series of cases, properly defined and adequately controlled, is essential before such a claim would be justified an ideal which is perhaps unattainable The senior author is enthusiastic about the effect of propranolol in both stable angina and impending infarction if it is given skillfully and in adequate dosage, as the results of the present study indicate However it is evident that the vast majority of patients survive the preinfarction syndrome on any medical treatment if put to rest at home or hospital usually without major new myocardial damage In the present series of 18 cases on propranolol which is larger than any of the series reported following saphenous vein graft bypass, the results were actually better than after surgical intervention The latter, therefore, we believe is not indicated in impending infarction Furthermore, no matter how experienced the surgeon there will probably be an operative mortality rate of at least 5 per cent in any large series of cases,[2] and as yet there is no proof that the operation prevents infarction or its extension The reported good results with operation may merely reflect those obtained on medical treatment. Exposing the patient to operative risk appears unwarranted at this time Indeed there is a possible theoretical objection to the operation at this stage angiographic studies have shown that, in some cases whether the vein graft remains patent or is closed the patient's own collaterals, previously demonstrated, are no longer evident.[31] If a coronary artery is narrowing progressively during the impending phase, as seems likely in some cases at least, it is important to allow collaterals to develop It is conceivable that inserting a saphenous bypass at this time may interfere with this process

It must be remembered that early closure of the vein graft (two weeks to four months) has been reported in up to 14 per cent of cases, and later occlusion up to 30 per cent [13,31] Closure of a major coronary artery proximal or distal to the bypass and myocardial infarction have also been reported postoperatively [31] Hence at present, vein graft bypass during impending infarction must be considered only an experimental procedure[32] which is probably unnecessary and also has some practical and theoretical drawbacks.

Although the findings may be different in a large group of cases it seems tenable to assume that the use of propranolol in our 18 cases of definite impending infarction is related to the excellent results obtained. It is a fact that the drug gives relief in a very large percentage of patients with stable anginal syndrome, even when the pain has been refractory to all other drugs Good results have been reported in up to 85 per cent of cases[14] and are even higher in the experience of the senior author Propranolol has numerous effects upon the heart its success in angina is achieved mainly by reducing myocardial oxygen demand and consumption,[33] although it has also been attributed to known anesthetic properties of the drug rather than to beta adrenergic blockade alone [34] It is probable that these beneficial effects of propranolol operate also during impending infarction [29] In experimental

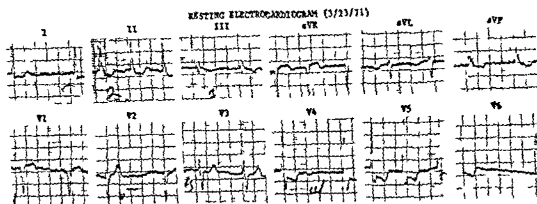


Fig 2. M C 75 year-old man Previous angina pectoris and atrial fibrillation. ECG otherwise negative ECG taken on 3/23/1971 shows impending infarction There are definite ST and T changes

myocardial infarction propranolol appears to lessen the extent of the infarction and use in that stage of the disease also has been suggested.[35] It is essential to give propranolol in adequate dosage which varies a great deal from person to person

Theoretical consideration of possible adverse effects of propranolol are not infrequently cited—e g increased coronary vascular resistance and decreased coronary flow impaired myocardial contractility and ventricular dilatation[33] However most investigators report that the beneficial physiological effects of the drug are greater than these and this is borne out by clinical experience In the present series of cases there was no clinical evidence of interference with cardiac function in any way and there appears to be little or no danger in using propranolol in impending infarction On the other hand, whether the 100 per cent excellent results in our cases are related to the drug remains an open question which requires confirmation

Summary

The prognosis in impending infarction is good on a medical regime of bed rest and sedation. In a series of 18 cases treated also with propranolol the results were even better there were no deaths or transmural infarction Surgical intervention is *not indicated* in impending infarction and should be considered an experimental procedure at this time

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Localized ventricular gradient of the papillary muscles

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The most important contribution to electrocardiography made by Wilson and associates[1] was the concept of the ventricular gradient Ashman and associates[2-6] followed with important studies in this field. These investigations and those of others have been concerned with the heart as a whole By taking advantage of electrocardiograms in which T waves were isoelectric the spatial vectorcardiogram of the ventricular gradient was derived.[6] No attempt has been made previously to obtain the ventricular gradient (G) for small localized segments of the heart This report is concerned with measurements of this nature for approximately 2 mm segments of the lateral papillary muscle and the lateral wall of the left ventricle from which the papillary muscle arose in the intact dog

Definition of the ventricular gradient has been presented previously[7] and, therefore need not be discussed in detail here Briefly it is an expression of variations in duration of the excited state—i e it is an expression of the differences in the time courses of the order of depolarization (electric activation) and the order of repolarization (electric regression) The ventricular gradient is represented by a vector electric quantity which has magnitude direction and sense Its direction is from the area of longest duration of the excited state to the area of shortest duration Its magnitude therefore is in units of time and voltage (micro or millivolt seconds)

As mentioned above Wilson and associates[1] and other investigators limited their applications of the concept of the ventricular gradient to the entire heart. The resultant ventricular gradient for the entire heart, however represents the mean for the innumerable small segments which constitute the myocardium The concept of a ventricular gradient is applicable to a sarcomere Such applications were not made in these investigations However the gradient was obtained for segments of the ventricle about 2 mm in size as described below

Materials and methods

Five healthy mongrel dogs weighing between 10 5 and 18 2 kilograms were anesthetized with sodium nembutal. After opening the chest by either midsternal incision or by incision in the fifth left intercostal space four multiple electrode needles were inserted into the left ventricle in the region of the anterolateral papillary muscle[8] The multiple electrode needles which were obtained from Dr D Durrer of the University of Amsterdam, consisted of 7 to 10 electrodes positioned 1 66 to 3 0 mm. apart. The spread of activation from one electrode to the next of each needle was recorded simultaneously on a 15 channel recorder designed and constructed in our laboratory Twelve channels recorded local electrical activity directly from the heart muscle one channel recorded Lead V_F of the electrocardiogram and the other two channels recorded the frontal and left sagittal plane projections of the spatial vectorcardiogram. The recordings were timed at 1 millisecond intervals

After control recordings were obtained for each multiple electrode needle ischemia of the

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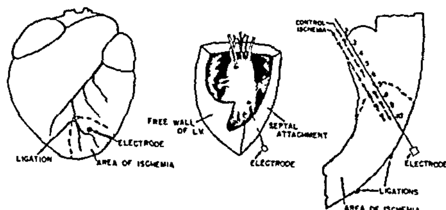
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LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE

DOG NO. 62



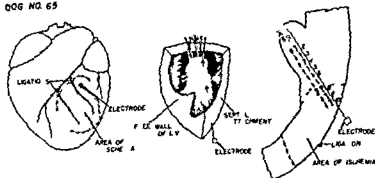
BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (mv sec)		VENTRICULAR GRADIENT MAGNITUDE (mv sec)		DIRECTION (Endo ⟵⟶ Epi)	
	Control	Ischemia	Control	Ischemia	Control	Ischemia	Control	Ischemia
1–2	+0.46	+0.24	0	0	+0.46	+0.24	←	→
2–3	+0.34	+0.19	−0.84	−0.24	−0.50	−0.05	?	?
3–4	−0.58	−0.29	−3.36	−0.24	−3.94	−0.53	→	←
4–5	−0.58	−0.24	−0.72	−0.24	−1.30	−0.48	→	←
5–6	+0.43	−0.36	−0.84	−2.04	−0.41	−2.40	?	→
6–7		+0.24		+1.68		+1.92		←
7–8	−0.22	+0.17	+0.24	+0.07	+0.02	+0.24	?	←
8–9	−0.65	−0.41	+0.24	+0.43	−0.41	+0.02	?	?
9–10	−2.16	−1.56	0	+3.12	−2.16	+1.56	→	?

Fig 1 This illustration indicates the local ventricular gradients for 2 mm segments of the papillary muscle and adjacent myocardium The diagrammatic sketch shows the site of the multiple electrode needle placement and the area of myocardial ischemia produced by ligations of the coronary arteries The arrows located along the needle indicate the direction of the ventricular gradient between the respective two adjacent electrodes (2 mm apart) for the control condition and again during myocardial ischemia The values for the magnitudes of the electrical forces associated with depolarization repolarization and the ventricular gradient during the control and ischemic states of the papillary muscle and adjacent myocardium are shown in the table The arrows in the table indicate the direction of the ventricular gradient When the ventricular gradient is oriented toward the endocardium the arrow is directed to the left and when it is oriented toward the epicardium the arrow is directed to the right The question marks indicate segments for which the direction of the ventricular gradient could not be determined. All six illustrations are similarly organized.

anterolateral papillary muscle was produced by ligation of the left anterior ventricular branches of the anterior descending coronary artery and the anterior branches of the left circumflex coronary artery [8] Recordings from the needles were again obtained at various intervals of time after ligation Immediately after the dog was killed the heart was removed and the exact locations of the needles and each electrode were carefully noted and recorded

To determine Ĝ of the papillary muscle, the recordings used were those obtained from the multiple electrode needle which was found to traverse best the papillary muscle when the heart was examined at the end of the study These curves recorded simultaneously for all bipolar positions of the needle, were obtained before ligation and again between 1¼ hours and 3¾ hours after ligation of the coronary arteries. The polarity of the multiple electrodes was such that a spread of the wave of activation from the epicardial region toward the endocardial region of the papillary muscle produced a positive or upward deflection of the recording and a wave spread from endocardial to epicardial regions produced a negative or downward deflection G was calculated as the algebraic sum expressed in millivolt seconds, of the areas (positive or negative) enclosed by the wave of depolarization and by the wave of repolarization as described previously [7] The direction of Ĝ was determined from polarity of the algebraic sum [9]

LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE



BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (m sec)		VENTRICULAR GRADIENT MAGNITUDE (mv sec)		DIRECTION (Endo ⟷ Epi)	
	Control	Ischem	Con	Ischemia	Control	Ischemia	Control	Ischemia
1–2	+0 60	+0 36	–0 96	–0 36	–0 36	0	?	none
–3	+0 43	0	+0 07	–6 96	+0 50	–6 96	←	→
3–4	+0 8	+1 49	–0 96	+6 48	–0 14	+7 97	?	←
4–5	+0 19	+0 05	–0 05	0	+0 14	+0 05	←	←
5–6	–0 02	–0 05	0	0	–0 02	–0 05	←	←
6–7	–0 86	–0 84	–0 84	–0 24	–1 70	–1 08	←	←
7–8	–0 72	–0 53	+0 91	+0 10	+0 19	–0 43		
8–9	–0 65	–0 72	+0 10	–0 19	–0 55	–0 91		←
9–10	–1 32	–0 91	+0 77	–0 77	–0 55	–1 68		←

Fig 2 Consult legend for Fig 1

Results

The results for the 5 dogs studied are summarized in Figs 1 to 6 It is evident from the illustrations and their respective tabulated data that the localized ventricular gradient varied in direction and magnitude at 2 mm intervals throughout the myocardium and papillary muscle along the length of the multiple electrode needle These data also indicate that there was no definite trend for the directions of G from one electrode site to the next in each anesthetized dog nor from one dog to another The magnitude of the local ventricular gradient varied from zero to 9 9 millivolt seconds

Myocardial ischemia produced by coronary artery ligation for a duration of one to almost four hours altered the direction and magnitude of the local ventricular gradients These changes were not consistent, however Although the magnitude changed for every local segment of myocardium the direction of G did not always change There were no apparent differences between the patterns of the local Ĝ of the myocardium of the papillary muscle itself and those of the lateral wall of the left ventricle from which the papillary muscle arose The overall tendency is for the local G for the normal heart to be directed from the epicardial to the endocardial surface in the free wall of the left ventricle But, within the papillary muscle itself there was no consistent, uniform direction of Ĝ

The magnitude of local G varied considerably following coronary artery ligation There was no apparent relationship between the magnitude of G and the location of the corresponding segment within the papillary muscle or within the free wall of the left ventricle from which the papillary muscle arose

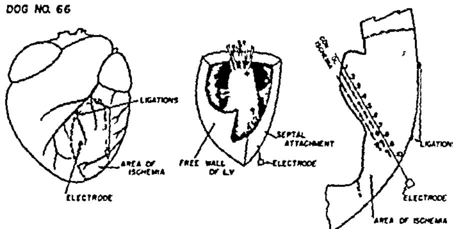
The direction of G following coronary artery ligation did not always change for every local site studied. There was no relationship between the change in direction and the change in magnitude of G produced by ischemia

Discussion

Although Wilson and associates[1] Ashman and colleagues[2,5] and others[10] applied the concept of the ventricular gradient to the heart as a whole

LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE

DOG NO. 66



BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (mv sec)		VENTRICULAR GRADIENT MAGNITUDE (mv sec)		DIRECTION (Endo ⟷ Epi)	
	Control	Ischemia	Control	Ischemia	Control	Ischemia	Control	Ischemia
1–2	0	+0.05	−2.16	0	−2.16	+0.05	[arrow]	[arrow]
2–3	+0.36	−0.07	+0.19	0	+0.55	−0.07	[arrow]	[arrow]
3–4	+0.29	+0.48	+0.48	−0.02	+0.77	+0.46	[arrow]	[arrow]
4–5	+0.36	+0.17	0	+0.14	+0.36	+0.31	[arrow]	[arrow]
5–6	+0.07	+0.24	0	+0.02	+0.07	+0.22	[arrow]	[arrow]
6–7	+0.12	+0.17	0	0	+0.12	+0.17	[arrow]	[arrow]
7–8	−0.05	+0.17	+0.05	+0.10	0	+0.27	none	[arrow]
8–9	−0.24	−0.67	+0.31	+1.56	+0.07	+0.89	?	?
9–10	−0.84	—	+0.48	—	−0.36	—	?	

Fig 3 Consult legend for Fig 1

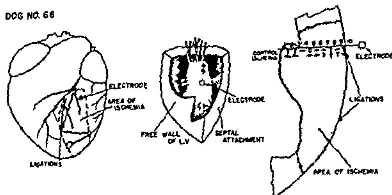
and expressed the gradient as a single vector the studies reported herein apply the concept of the ventricular gradient to small segments of the myocardium G could be obtained for a sarcomere as well, if a recording of the time courses of depolarization and repolarization were obtained. Using the multiple electrode needle with bipolar electrode intervals of about 2 mm the ventricular gradients of the myocytes or sarcomeres in the vicinity of the bipolar electrodes were obtained When the heart is considered as a whole and only the mean ventricular gradient is recorded, its direction is from the endocardial surface to the epicardial surface but this study shows that within sharply localized segments of the myocardium of five dogs the ventricular gradients for small segments of the papillary muscles simultaneously varied from area to area Myocardial ischemia produced by ligation of the coronary arteries supplying the papillary muscle and the area of the wall of the left ventricle from which the papillary muscle arose changed the magnitude but not necessarily the direction of the ventricular gradient for all localized areas studied

Studies of this sort[8,12,13] in which a needle is plunged into the myocardium must alter the myocardium locally to some degree Galvanic currents of fairly large magnitude were produced immediately with insertion of the needles It was necessary to wait 30 minutes or more for the galvanic effects to subside and for the recordings to stabilize Furthermore the dogs were anesthetized and their chests were open with the hearts exposed to the atmosphere even though they were covered with soft towels moistened with Ringer s solution The influence of these factors as well as of others is not known and could not be evaluated. Nevertheless these experiments do reveal a method for obtaining local ventricular gradients for the physiologic state of the heart at the moment These findings reveal the gross nature of the ventricular gradient as previously applied to the entire heart

One can only wonder why the time courses of the order of electrical activation and regression and, therefore, the ventricular gradient should be as found for the papillary muscle and adjacent free wall of the left ventricle The relationship of these sharply localized electric phenomena to

LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE

DOG NO. 66

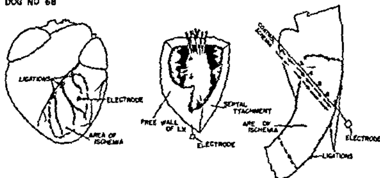


BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (m sec)		VENTRICULAR GRADIENT			
					MAGNITUDE (mv sec)		DIRECTION (Endo → Epi)	
	Control	Ischemia	Control	Ischemia	Control	Ischemia	Control	Ischemia
1–2	+ 1 32	+ 1 68	– 0 84	+ 0 12	+ 0 48	+ 1 80	?	←
2–3	+ 0 84	+ 1 68	– 0 72	– 0 05	+ 0 12	+ 1 63	?	←
3–4	– 0 43	– 0 34	– 0 72	+ 0 91	– 1 15	+ 0 57	←	?
4–5	0	– 5 76	0	– 0 43	0	– 6 19	none	→
5–6	– 0 67	+ 0 12	– 1 68	0	– 2 35	+ 0 12	←	←
6–7	– 1 15	– 0 19	– 0 48	+ 3 05	– 1 63	+ 2 86	←	?
7–8	– 1 08	– 0 36	+ 3 29	+ 1 92	+ 2 21	+ 1 36	?	?
8–9	– 1 44	– 1 10	– 2 16	+ 0 55	– 3 60	– 0 55	→	?
9–10	– 0 48	– 0 33	+ 1 44	– 1 44	+ 0 96	– 1 97	?	←

Fig 4 Consult legend for Fig 1

LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE

DOG NO 68

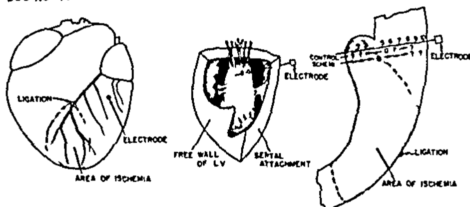


BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (mv sec)		VENTRICULAR GRADIENT			
					MAGNITUDE (mv sec)		DIRECTION (Endo → Epi)	
	Control	Ischemia	Control	Ischemia	Control	Ischemia	Control	Ischemia
1–2	+ 0 36	+ 0 36	– 3 72	– 8 16	– 3 36	– 7 80	?	→
2 3	+ 1 20	+ 1.27	+ 4 08	+ 8 64	+ 5 28	+ 9 91	←	←
3–4	– 0 17	– 0 12	– 6 12	– 1 20	– 6 29	– 1 32	→	←
4–5	+ 0 48	0	+ 2 52	– 0 84	+ 3.00	– 0.84	←	←
5–6	– 1 44	– 1 10	– 0 36	– 0 19	– 1.80	– 1.29	←	←
6–7	2 45	– 1 68	– 0 72	– 0 36	– 3 17	– 2.04	←	←

Fig 5 Consult legend for Fig 1

LOCAL VENTRICULAR GRADIENT OF PAPILLARY MUSCLE

DOG NO 71



BI POLAR ELECTRODES	DEPOLARIZATION (mv sec)		REPOLARIZATION (mv sec)		VENTRICULAR GRADIENT MAGNITUDE (mv sec)		VENTRICULAR GRADIENT DIRECTION (Endo ←→ Epi)	
	Control	Ischemia	Control	Ischemia	Control	Ischemia	Control	Ischemia
1—2	+0 19	+0 43	−2 40	0	−2 21	+0 43	?	←
2—3	+0 41	+0 60	−0 29	+0 05	+0 12	+0 65	?	←
3—4	+0 48	+0 24	0	+0 02	+0 48	+0 26	←	←
4—5	+0 05	0	0	0	+0 05	0	←	none
5—6	0	−0 07	0	−0 02	0	−0 09	no ←	←
6—7	−0 48	−1 68	+0 19	−0 43	−0 29	−2 11	?	→
7—8	−1 13	−1 13	−1 37	−0 79	−2 50	−1 92	→	→
8—9	−1 68	−2 64	+2 16	+2 40	+0 48	−0 24	?	?
9—10	−1 51	−2 23	+1 44	+3 60	−0 07	+1 37	?	?

Fig 6 Consult legend for Fig 1

those of other areas of the myocardium must be important for satisfactory myocardial function These relationships should be studied for the human heart A great volume of such data for the ventricular gradient could be obtained from the recordings of Scher and Durrer and associates [11-13] The influence of drugs disease metabolic disturbances and many other phenomena and agents that may modify the localized electrical activity of the myocardium the conduction tissue, and the nervous systems within the myocardium need investigation

Summary

Ventricular gradients $\hat{G}$ were obtained for sharply localized areas of the lateral papillary muscle and the adjacent free wall of the left ventricle of five dogs The ventricular gradients recorded for 2 mm segments of myocardium varied considerably in magnitude and direction Myocardial ischemia changed the magnitude of the G for all areas studied, but did not always change the direction The method and concept described are applicable to the study of the influence of drugs disease, neurogenic and physical factors, as well as other factors on local G of the myocardium of experimental animals and man

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Systolic time intervals during submaximal and maximal exercise in man*

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The assessment of changes in systolic time intervals (STI) in individuals with a wide variety of cardiovascular disorders, and following various physiologic and pharmacologic interventions, has been extensively documented as discussed in recent reviews of the subject.[1-5] It has been shown that these noninvasive measurements correlate well with more direct internal measurements of left ventricular performance,[6-11] despite the fact that there are multiple determinants for each of these intervals

Exercise testing in cardiology has been primarily employed for demonstrating the presence of significant coronary atherosclerotic heart disease by the appearance of electrocardiographic (ECG) evidence of myocardial ischemia or angina type chest pain It has recently been suggested that the response of the STI to exercise may offer a new approach to stress testing in patients with heart disease and several studies describing alterations in STI in these patients have been reported[12-20] In most of these latter studies, however recordings of STI were made during the recovery period following low intensity exercise of rather brief duration[12,14,15,18,19] In addition, STI measurements obtained during or following exercise were corrected for heart rate utilizing regression equations derived from resting data[14,15,17,18] There are few data available concerning regression equations derived from a wide range of heart rates in supine exercising subjects

The purpose of the present study was (1) to describe the response of the STI during the course of prolonged submaximal and short duration maximal exercise to exhaustion in normal individuals (2) to establish normal regression equations relating changes in STI with increasing heart rate during both levels of exercise stress and (3) to compare regression equations relating all the STI with heart rate during exercise with similar data obtained in the resting state

Materials and methods

Subjects and test procedure Ten young physically active men served as volunteer subjects The mean (±S E) age and body surface area of this group were 19 8 ± 0 5 years and 1 84 ± 0 04 M², respectively All had undergone directed history, physical examination and exercise testing to assure normality and to exclude clinically recognizable pulmonary, cardiovascular and musculoskeletal disorders The men were studied in the supine posture during periods of rest and exercise on a foam padded x ray table to which a constant load bicycle ergometer (Quinton 844) was attached The pedal axle was located 36 cm above the table the stroke radius was 17 cm. Subjects were positioned in a manner which permitted only a slight bend at the knee i e, somewhat less than complete extension when the pedal was in the most distal position A shoulder restrainer and hand grips were

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employed to maintain optimal contact with the pedals and to minimize movement above the waist. Athletic shorts, socks and tennis shoes were worn during periods of study Ambient temperature was maintained at 22 C

Preliminary tests were conducted with each subject to establish a work load which would effect a heart rate (HR) of about 130 beats per minute after 10 minutes of supine exercise Thereafter two different subjects were studied without sedation and in the postabsorptive state each morning for five consecutive days Exercise was performed at the predetermined submaximal load (700 to 900 Kg M per minute) at a pedal rate of 60 r p m until exhaustion occurred. A week later the subjects performed maximal or high intensity (1 200 to 1 600 Kg M per minute) short duration exercise to exhaustion according to the above protocol Exhaustion was defined as the inability to maintain pedal rate despite strong encouragement and high investigator induced motivation to continue

Instrumentation and measurements An ECG lead with an active electrode on each of the midaxillary lines and a ground on a thoracic vertebra yielding a discrete Q wave was recorded. A contact microphone (Hewlett Packard 21050A/B) with a frequency response between 0 02 and 2000 Hz and a time constant of 2 sec with a 2 megohm impedance was placed at the position where the aortic component of the second heart sound was most clearly defined and was strapped to the chest. This position was either the second or third intercostal space at the left sternal border Amplification of the transducer signal was provided by a heart sound preamplifier (Sanborn 350 1700C) having a flat frequency response range (±3 db) of 25 to 1 000 Hz A carotid arterial tracing was obtained with a funnel shaped pulse pickup (H P 21051D) with a flat frequency response of 0 1 to 40 Hz and a time constant of <3 sec. The transducer was manually positioned over the point of maximal pulsation of the left carotid artery between the sternoclavicular joint and the angle of the jaw with the subject s face turned slightly toward the right shoulder The output of the transducer was amplified by a high gain preamplifier (Sanborn 350 2700C) with a band pass filter setting of 0 15 to 40 Hz.

The ECG phonocardiogram and carotid pulse tracing were displayed on an oscilloscope (H P 760) to explore those regions which afforded the technically best tracings and were recorded simultaneously at 100 or 200 mm. per second paper speed on a multichannel light sensitive recorder (Honeywell 1508) Recordings were made at rest during the course of exercise just prior to the cessation of pedaling and in the immediate recovery period.

Total electromechanical systole (QS_2) was measured from the onset of the Q wave of the ECG to the first high frequency vibration of the aortic component of the second heart sound. The left ventricular ejection time (LVET) was measured from the onset of the rapid rise of the carotid pulse tracing to the nadir of its incisura The pre ejection period (PEP) i e the interval from the onset of ventricular depolarization to the beginning of left ventricular ejection was derived by subtracting the LVET from the QS_2 interval All intervals were determined as the average of measurements of at least five and generally ten consecutive beats, each read to the nearest 5 msec Heart rate was derived by dividing the average R R interval into 60

Statistical methods Arithmetic plots of the systolic time intervals vs heart rate for each individual appeared to be linear between the exercise limits of 120 and 160 beats per minute but generally levelled off at heart rates greater than 170 beats per minute suggestive of exponential behavior Accordingly the data for each individual were least square fitted to an arithmetic straight line a single exponential (semilog straight line) and a second degree polynomial to determine the best functional fit on the basis of three curve fitting criteria standard deviation from regression correlation coefficient and significance of the slope (applicable only to semilog and arithmetic plots) Intercept comparisons were not accepted as criteria because they imply comparisons of extrapolated values far outside the experimental range

The second degree polynomial fit possessed a very large standard deviation from regression and was rejected. On the average the correlation coefficients significance of slopes and standard deviations from regression for the semilog fit were slightly better than those for the linear fit. However omission of the few data points beyond HR = 170 beats per minute sufficiently reduced the disparity between the two fits to render them essentially indistinguishable for the practical purpose of demonstrating significant differences among the various experimental categories in

Table I Mean (±S E) workload heart rate at rest and exhaustion, and endurance time for submaximal and maximal supine bicycle exercise

	Workload (Kg M/min.)	Heart rate* Rest	Heart rate* Exhaustion	Endurance time (min.)
Submaximal				
Mean	830	59	155	78 0
SE	21	2	4	12 3
Maximal				
Mean	1320	61	171	5 0
SE	33	4	4	0 5

Beats per minute

Table II Regression data* relating the systolic time intervals to heart rate during submaximal and maximal supine bicycle exercise

Systolic interval	Regression equation	SDR	Correlation coefficient (r)	Significance of slope
Submaximal				
QS_2†	QS_2 = 571 2 071 HR	11	0 92	P < 0 001
LVET	LVET = 451 1 701 HR	10	0 91	P < 0 001
PEP	PEP = 116 0 339 HR	9	0 48	P < 0 001
Maximal				
QS_2	QS_2 = 490 1 373 HR	9	0 91	P < 0 001
LVET	LVET = 434 1 416 HR	13	0 87	P < 0 001
PEP	PEP = 92 0 166 HR	6	0 29	NS

Regression data are expressed in milliseconds
†QS_2 = total electromechanical systole PEP = pre ejection period LVET = left ventricular ejection time HR = heart rate in beats per minute
SDR = standard deviation from regression.

the HR range of 120 to 170 beats per minute While the semilog fit appeared to be the technically better least square fit of the data, especially for studies involving HR > 170 beats per minute, the advantage of being able to compare the data with the linear regression data of previous investigators was felt to outweigh the slight improvement in accuracy its use entailed The final results and conclusions for the range in question are not materially affected by the choice of fit However, for studies at HR >170 this experience suggests the single exponential fit to be the method of choice

Inspection of the individual slopes over the linear range for each subject, and of the mean slope and standard deviations for each of the six categories (submaximal and maximal exercise QS_2, LVET, and PEP) revealed a reasonably constant behavior indicating that the data formed a homogenous population with respect to heart rate and could be pooled T testing of the individual slopes against the mean slope for each category showed no significant differences reinforcing this conclusion Accordingly the subject data were grouped into six categories (QS_2 LVET and PEP under submaximal and maximal conditions) and the best least squares fit to a straight line determined for each situation Large correlation coefficients and highly significant slopes were found for both maximal and submaximal QS_2 and LVET providing further justification for pooling the data All statistical methodology followed Snedecor[21] and a Mathatron 4280 TPL Minicomputer was used

Results

Mean work loads heart rates at rest and exhaustion, and times to exhaustion for submax

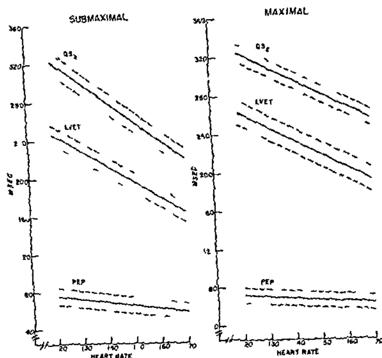


Fig 1 The relationship of the phases of systole measured during submaximal (left panel) and maximal (right panel) exercise to heart rate Broken lines represent ± 1 S D

Table III Comparison of slopes and intercepts of systolic time intervals during submaximal and maximal exercise

Systolic interval	Difference in slopes	Difference in intercepts
QS_2	P < 0 001	P < 0 001
LVET	NS	P < 0 001
PEP	NS	P < 0 001

imal (submax) and maximal (max) levels of exercise are presented in Table I The heart rate (HR) of 155 beats per minute at a mean exhaustion time of 78 minutes with submax exercise was significantly lower (P < 0 01) than the exhaustion heart rate of 171 beats per minute with max exercise which lasted an average of 5 minutes

Table II and Fig 1 show the dependence of the systolic time intervals on heart rate The duration of QS_2 and LVET are related inversely and linearly to heart rate The fit of these intervals to a straight line appears very good for both submax and max levels of exercise While the correlation coefficient for submax exercise PEP (submax PEP) is small it is still significantly different (P < 0 001) when tested against no correlation In contrast, the correlation coefficient for max exercise PEP is small, not significantly different from zero, and the slope is not significant The inference here is that on the average max PEP does not appear to be a function of HR i e it is constant over the range of 120 to 170 beats per minute Inclusion of data at both ends of the range could change this behavior to what was found for submax exercise PEP An early decrease in the PEP/LVET ratio was observed from rest to exercise Because the LVET continued to shorten during both levels of exercise while the PEP either changed slightly (submax exercise) or remained unchanged (max exercise) the ratio of the PEP to LVET increased in most cases

Table IV Comparison of mean (± S E) values of heart rate LVET and PEP at end exercise and during immediate recovery from submaximal endurance exercise

	Heart rate	LVET	PEP
Exercise	157 ± 5	183 ± 7	66 ± 3
Recovery*	135 ± 8	198 ± 9	62 ± 4
P	< 0 001	< 0 05	< 0 05

*N = 7 subjects

Table I Mean (±S.E.) workload heart rate at rest and exhaustion, and endurance time for submaximal and maximal supine bicycle exercise

	Workload (kg. M/min.)	Heart rate*		Endurance time (min.)
		Rest	Exhaustion	
Submaximal				
Mean	830	59	155	78.0
SE	21	2	4	12.3
Maximal				
Mean	1320	61	171	5.0
SE	33	4	4	0.5

*Beats per minute

Table II Regression data* relating the systolic time intervals to heart rate during submaximal and maximal supine bicycle exercise

Systolic interval	Regression equation	SDR	Correlation coefficient (r)	Significance of slope
Submaximal				
QS_2†	QS_2 = 571 2.071 HR	11	0.92	$P < 0.001$
LVET	LVET = 451 1.701 HR	10	0.91	$P < 0.001$
PEP	PEP = 116 0.339 HR	9	0.48	$P < 0.001$
Maximal				
QS_2	QS_2 = 490 1.373 HR	9	0.91	$P < 0.001$
LVET	LVET = 434 1.416 HR	13	0.87	$P < 0.001$
PEP	PEP = 92 0.166 HR	6	0.29	NS

*Regression data are expressed in milliseconds.
†QS_2 = total electromechanical systole. PEP = pre ejection period. LVET = left ventricular ejection time. HR = heart rate in beats per minute.
SDR = standard deviation from regression.

the HR range of 120 to 170 beats per minute. While the semilog fit appeared to be the technically better least square fit of the data especially for studies involving HR > 170 beats per minute, *the advantage of being able to compare* the data with the linear regression data of previous investigators was felt to outweigh the slight improvement in accuracy its use entailed. The final results and conclusions for the range in question are not materially affected by the choice of fit. However, for studies at HR > 170 this experience suggests the single exponential fit to be the method of choice.

Inspection of the individual slopes over the linear range for each subject, and of the mean slope and standard deviations for each of the six categories (submaximal and maximal exercise QS_2, LVET, and PEP) revealed a reasonably constant behavior, indicating that the data formed a homogenous population with respect to heart rate and could be pooled. T testing of the individual slopes against the mean slope for each category showed no significant differences reinforcing this conclusion. Accordingly, the subject data were grouped into six categories (QS_2, LVET, and PEP under submaximal and maximal conditions) and the best least squares fit to a straight line determined for each situation. Large correlation coefficients and highly significant slopes were found for both maximal and submaximal QS_2 and LVET, providing further justification for pooling the data. All statistical methodology followed Snedecor[21] and a Mathatron 4280 TPL Minicomputer was used.

Results

Mean work loads, heart rates at rest and exhaustion, and times to exhaustion for submax

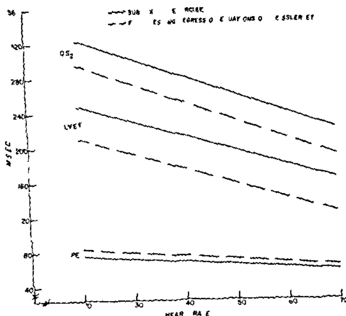


Fig 2 Comparison of submaximal exercise curves with resting curves of Weissler and associates[1] relating the systolic time intervals and heart rate

Large and significant (P < 0 001) decreases occurred in each of the phases of systole between rest and HR = 120 beats per minute i e within the first few minutes of submaximal exercise and in less than one minute of maximal exercise Decreases in mean QS_2 LVET and PEP of 99 0 64 1 and 35 4 msec respectively for submaximal exercise and 90 6 46 2 and 33 4 msec respectively for maximal exercise were found between rest and HR = 120 beats per minute

Comparison of the submaximal exercise curves of Fig 1 with those calculated from the resting regression equations of Weissler and associates[1] relating the systolic time intervals and heart rate for normal men is given in Table VI and Fig 2 The slopes for QS_2 and LVET with the increase in heart rate accompanying submax exercise are identical with the resting regression equations of Weissler and colleagues[1] relating these intervals and heart rate However the intercept values for the submax exercise regression lines are significantly greater than those calculated with Weissler and colleagues equations In contrast the intercept of the submax exercise regression line for PEP is less than Weissler and colleagues value while the slopes were essentially the same Resting measurements of each of the three systolic intervals in our 10 subjects fell well within the normal range defined in Weissler and colleagues regression data[1] which were derived from observations on 121 normal men during supine rest Despite the similarity in measurements experimental conditions were not entirely comparable since the feet of our subjects unlike those of Weissler and colleagues subjects were in contact with the ergometer pedals while recordings were being obtained It appears therefore that elevation of the legs during supine rest has little effect on the duration of the systolic intervals

Discussion

In the present study noninvasive indirect parameters of left ventricular function were utilized to assess the hemodynamic responses of 10 healthy young adult men during prolonged submaximal and short duration maximal supine leg exercise to exhaustion

Results of the study show that the hemodynamic response to both submaximal and maximal exercise as assessed by serial changes in the systolic time intervals (STI) was uniform among the 10 normal test subjects It was observed that within the heart rate range of 120 to 170 beats per minute total electromechanical systole (QS_2) and left ventricular ejection time (LVET) were related inversely and linearly to heart rate for submaximal and maximal exer

Table V Comparison of resting values of systolic intervals calculated from regression equations with measured resting intervals

Exercise	Mean difference of (exp calc)	SDR	Behavior of curve with respect to resting data
Submaximal			
QS_2	-27 0	11	Overestimates by 6 4%
LVET	-39 5	10	Overestimates by 13%
PEP	14 8	9	Underestimates by 13%
PEP/LVET	0 084		Underestimates by 24%
Maximal			
QS_2	10 1	9	Underestimates by 2 4%
LVET	-37 1	13	Overestimates by 12%
PEP	23 4	8	Underestimates by 22%
PEP/LVET	0 105		Underestimates by 31%

Table VI Comparison of exercise regression equations with regression equations of Weissler and associates[1]

Curve	Intercept	Slope	SDR
Weissler QS_2	546	-2 1	14
This study QS_2 Submax	571	-2 1	11
QS_2 Max	490	-1 4	9
Weissler LVET	413	-1 7	10
This study LVET Submax	451	-1 7	10
LVET Max	434	-1 4	13
Weissler PEP	131	-0 4	13
This study PEP Submax	116	-0 34	9
PEP Max	92	-0 17	8

A comparison was made of the submaximal and maximal values of QS_2 LVET and PEP A t test of slopes and intercepts established the differences presented in Table III While the QS_2 LVET and PEP had significantly different intercepts during maximal as compared with submaximal exercise the slopes of the regression lines relating the intervals to HR differed significantly only for the QS_2

Table IV compares mean (±S E) values for HR LVET and PEP at the end of the submax exercise run with those values recorded in the immediate post exercise recovery period In this group of subjects there was a significantly higher mean HR (+22 b p m) longer LVET (+10 msec) and shorter PEP (−4 msec) in the immediate postexercise period as compared to values obtained just prior to the cessation of pedaling

Comparison of exercise curves with resting data The linear STI curves for the HR range of 120 to 170 beats per minute were compared with two available kinds of resting data—the resting values measured during these experiments and the linear resting regression data of Weissler and colleagues[1] Using the linear relationships of Table II STI were computed from resting heart rates and the results compared with the measured time intervals The results are summarized in Table V It is seen that only the calculated max exercise QS_2 values agree with the experimental values to 1 S D Calculated submax exercise QS_2 submax exercise LVET and max exercise LVET values were consistently larger than the measured values by two to four times the standard deviation from regression Because the data used to construct the least squares lines corresponded to heart rates of 120 to 170 beats per minute the failure to predict resting rates corresponding to 50 to 60 beats per minute demonstrates the risk inherent in extrapolating beyond one's data range

increased activity of the sympathetic nervous system during exercise Thus the inotropic effect of exercise resulting from increased adrenergic stimulation is achieved early in exercise and continues to exert a positive influence on left ventricular performance until exhaustion supervenes It appears that with maximal exercise the peak inotropic effect is attained early and thereafter remains relatively constant whereas in submaximal exercise the inotropic influences on the left ventricular myocardium may continue to increase slightly throughout the period of exercise

The regression lines for submaximal exercise were compared with the resting regression lines of Weissler and colleagues[1] relating the STI with a wide range of resting heart rates The shortening in QS_2 and LVET with the increase in heart rate accompanying submaximal exercise followed the slopes of the resting regression equations relating these intervals and heart rate However the regression lines for both QS_2 and LVET were at significantly higher levels during exercise In this study there was a shortening of the PEP beyond that expected for rate as derived from the resting regression equations Thus supine exercise markedly alters the relationship between left ventricular STI and HR as expected from resting regression formulas The findings demonstrate the invalidity of regression equations derived from resting heart rates in the evaluation of responses to exercise

It is appreciated that any explanation of the observed changes in the STI herein reported must be speculative since direct measures of concurrent hemodynamic changes had not been made However since circulatory changes in normal man during supine exercise have been reasonably well documented in previous studies using the techniques of cardiac catheterization[31-33] available information from these sources does permit an analysis of the changes in the STI relative to heart rate in terms of the variables shown to affect the duration of the phases of the cardiac cycle

Summary

This study describes the serial responses of the systolic time intervals (STI) to submaximal and maximal supine exercise in normal subjects. Regression equations relating STI and heart rate during supine submaximal and maximal exercise are derived. It is shown that within the heart rate range of 120 to 170 beats per minute total electromechanical systole (QS_2) and left ventricular ejection time (LVET) are related inversely and linearly to heart rate for both levels of exercise At comparable heart rates the QS_2 and LVET are greater during maximal than submaximal exercise with differences widening significantly with increasing heart rate This finding points out the importance of taking into account the intensity of exercise when evaluating STI responses to exercise stress in different groups

The pre ejection period (PEP) significantly decreases from rest to the initial phase of both maximal and submaximal exercise with a subsequent tendency to plateau, indicating that a minimum PEP is reached early during exercise and that cardiovascular adaptation no longer includes additional shortening

This study also shows that STI obtained during exercise cannot be corrected for heart rate according to regression equations which were developed in resting supine subjects Thus there appears to be no justification for extrapolating the heart rate range of resting supine subjects to the exercise state for correcting intervals in this manner In addition STI measurements made during the immediate recovery period following supine exercise are significantly different from those obtained just prior to cessation of exercise Therefore recovery STI do not reflect the true hemodynamic changes occurring during the course of exercise

The application of the levels of exercise described in this study to the assessment of changes in STI in patients with documented or suspected cardiac dysfunction appears warranted. Alterations in left ventricular performance not evident at rest or following mild exercise might be detected employing these more strenuous exercise protocols Using the regression equations established in this study exercise induced deviation in STI corrected for heart rate may now be determined with the realization that these relationships were derived from relatively young men However in the adult population the duration of LVET corrected for heart rate varies little with advancing age and PEP shows only a slight increase[34,35]

The authors are indebted to Mr Barry L. Bates for his able technical assistance and to Dr Arnold M. Weissler for rendering valuable advice in the preparation of this manuscript

cise The small standard deviations from regression, high correlation coefficients, and significance of slopes for both QS_2 and LVET with both levels of exercise indicated that all 10 subjects in this study formed a homogeneous population from which valid conclusions could be drawn The diminution in QS_2 with increasing heart rate for both submaximal and maximal exercise reflects a summation of a large negative slope of the LVET and either a lesser negative slope (submax) or no significant slope (max) of the pre ejection period (PEP) Previous studies have shown that increases in heart rate occurring with exercise induced pharmacologically, or by atrial pacing are accompanied by an abbreviation of QS_2 and LVET [12 20 22 23] Abbreviation of the PEP accompanies an increase in heart rate induced by adrenergic stimuli, but not by para sympathetic blockade or atrial pacing [23 5] In the present study there was a large and significant decrease in QS_2 LVET and PEP from rest to the initial phase of exercise (HR = 120) As exercise continued there was a further increase in heart rate which was accompanied by further shortening of the systolic intervals except for PEP during maximal exercise However the measured QS_2 and LVET for heart rates over 170 beats per minute attained by one subject (L T) departed from linearity and appeared to become a curvilinear function This finding suggests that the correct dependence of QS_2 and LVET on heart rate over a wider range than reported here is perhaps a double exponential The likelihood of such a relationship with respect to total systole is reinforced by the work of Strandell [26] who found that during exercise with stepwise increased workloads mechanical systole at first decreased approximately linearly with increasing heart rate but at high heart rates demonstrated a significant curvilinearity with successively lesser decrease of mechanical systole Data from the present material were insufficient to merit more sophisticated analysis, but indicated the desirability of extending measurements to heart rates greater than 170 beats per minute, where possible, and to look for a double exponential data fit The latter could have a significant effect on physiological interpretation and model building

It has been shown that the LVET varies directly with enhanced ventricular filling stroke volume, and afterload, and inversely with heart rate and myocardial inotropy [6 8 27] While the augmentation of venous return by maximal and submaximal exercise tends to prolong the LVET the positive inotropic effects of exercise induced by adrenergic cardiostimulation tend to abbreviate it Jones and Foster[12] studied the factors governing the duration of left ventricular ejection and found heart rate to be the major determinant of ejection time during supine leg exercise The progressive fall in LVET observed in this study during maximal and submaximal exercise appears compatible with these findings

It was of considerable interest to compare the STI responses in the 10 subjects during submaximal with maximal exercise The functional relationships for QS_2 during maximal and submaximal exercise had significantly different slopes and intercepts by t test While the functional relationships for LVET during maximal and submaximal exercise had significantly different intercepts the slopes did not differ The physiological mechanism for the longer LVET among subjects during maximal exercise than during submaximal exercise may invoke several explanations The longer LVET during maximal exercise may reflect a higher stroke volume at comparable heart rates than attained with submaximal exercise [28] Moreover it has been shown that there is a progressive increase in systolic diastolic and mean arterial pressure with graded exercise as one approaches maximal performance [29] Hence peripheral resistance may be higher at comparable heart rates in maximal as compared with submaximal exercise also tending to increase LVET in the former

The PEP in this study showed a significant decrease from rest to the initial phase of exercise with a subsequent tendency to level off as exercise progressed to the endpoint of exhaustion While submaximal exercise PEP showed a linear correlation with heart rate on the average decreasing slightly with increasing heart rate maximal exercise PEP on the average showed no such correlation and appeared to remain constant with respect to heart rate in the reported range As previously mentioned changes in PEP reflect most consistently changes in the inotropic state of the left ventricle Braunwald and associates[30] observed a striking augmentation of the maximum rate of ventricular pressure during low intensity supine exercise of brief duration They interpreted this finding as a reflection of increased myocardial contractility mediated by the

Clinical and hemodynamic evaluation of coronary collateral vessels in coronary artery disease

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The significance of coronary collateral vessels associated with obstructive coronary artery disease remains subject to considerable debate despite numerous postmortem and clinical studies[1-7] Their anatomic existence has been documented[8-13] in all human hearts although they do not become functional unless there is a stimulus presumably myocardial ischemia which causes them to enlarge and become patent[1,8,9,14,15] When they are greater than 100 micra in diameter they can also be visualized during routine coronary arteriography[8,16,17] which permits the most physiologic estimate of their presence and potential value

Since controversy exists over what effect collateral channels have on the various clinical expressions of coronary heart disease and on left ventricular performance a consecutive series of patients with coronary artery disease was studied Patients with severe coronary obstructive disease with or without angiographically documented collaterals were compared clinically hemodynamically and angiographically to appraise the functional significance of these vessels

Methods

Seventy eight consecutive patients with angina pectoris and at least 75 per cent occlusion of a major coronary artery were studied by cardiac catheterization selective coronary arteriography and left ventriculography by standard techniques[18] The patients were separated into two groups according to the presence or absence of coronary collateral vessels

In addition to routine historical and physical examination each patient has chest roentgenograms a 15 lead resting electrocardiogram (ECG) and a biochemical profile The history of angina pectoris was graded on a scale from 1 to 4 Grade 1 being angina with mild exertion and Grade 4 being angina at rest or crescendo angina Any history of previous myocardial in

Table 1 Data for 78 patients

	No collaterals	*Collaterals*
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Treadmill exercise ECG % POS	91%	80% (P < 0 8)
Pacing VFC % abnormal	60%	96% (P < 0 01)
Mean coronary score	6 26 ± 0 45 (S E M)†	8 00 ± 0 38 (S E M) (P = 0 05)
Abnormal left ventriculogram	53%	90% (P < 0 025)

VFC entricular funct n curve
†S E M = standard erro of the mean

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Abnormal left ventriculogram	[illegible]3%	90% (P < 0 025)

*VFC = ventricular function curve
†S E M = standard error of the mean

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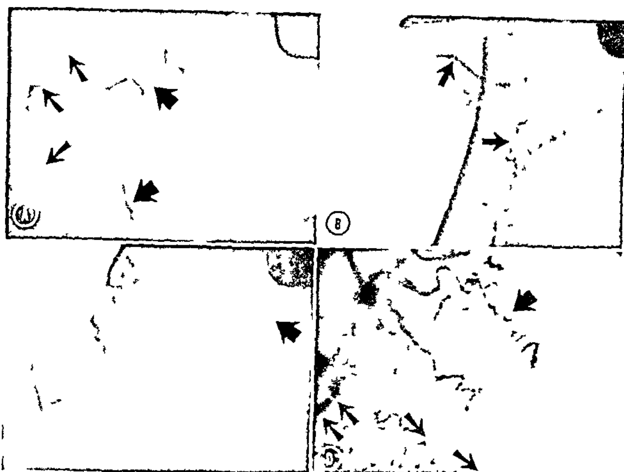


Fig 1 Examples of various types of collateral channels on single frames from 35 mm coronary cineangiograms. A Bridge collateral between the proximal and distal portions of the right coronary artery (large arrow) via atrial branches (small arrows) B Intercoronary collateral from proximal right coronary artery via conus branch (vertical arrow) to a branch of the left anterior descending artery (horizontal arrow) C Indirect evidence for collateral Left anterior descending (LAD) fills (arrow) from injection into right coronary artery without angiographically detectable collaterals D Multiple collaterals Bridge collaterals (large arrow) between proximal and distal LAD intercoronary collaterals between left and right coronary arteries (double arrow) and left to left collaterals between LAD and a branch of the left circumflex artery (small separated arrows)

farction was noted This diagnosis was based on history ECG and enzymatic data

A multistage treadmill exercise test was performed according to the method of Bruce and associates[20-23] with continuous ECG monitoring A positive ischemic response was judged only by objective data the J junction became depressed at least 1 mm below the control level and was accompanied by a flattened or downward sloping S T segment that persisted for at least 0 08 second Thus the S T segment subtends an angle of at least 90 degrees with the descending limb of the R wave The base line was established by the P R segment

Right atrial pacing was performed during the cardiac catheterization prior to the angiographic studies and pacing ventricular function curves were constructed relating changes in left ventricular end diastolic pressure (LVEDP) to changes in stroke work (SW)[24-28] Stroke work in gram meters was calculated from the following formula

$$SW = \frac{(BAm - LVEDP) \times SV \times 1.36}{100}$$

where BAm mean brachial artery pressure and SV = stroke volume The slope of the pacing ventricular function curve was analyzed as previously described[28] to estimate myocardial function

The degree of obstruction in each of the three main coronary arteries was classified according to the percentage of lumen occlusion and was divided into four groups for determining a coronary score A score of 1 meant that a vessel had less than 50 per cent obstruction a score of 2 obstruction between 50 and 75 per cent obstruction of greater than 75 per cent a score of 3 and total occlusion (100 per cent) as score of 4 The frequency of single double and triple vessel disease was determined for each group

The extent of obstructive disease for each of the two groups of patients was determined by taking the mean coronary score the scores of the two groups were then compared statistically by Student t test analysis

Collateral anastomoses were defined as being either intracoronary or intercoronary vessels In tracoronary collateral anastomoses were those vessels which bypassed an obstruction and caused opacification of the parent artery or the area of myocardium usually served by that artery distal to the site of obstruction after injection of contrast material into the same artery This type of connection has also been referred to as a bridge anastomosis[6]

Intercoronary vessels were those angiographically visible anastomoses between the artery injected and a contralateral vessel or the area served by that vessel Indirect evidence was also used to infer the presence of collateral vessels not directly visible This occurred when there was opacification of a coronary artery distal to the site of a high grade occlusion after the injection of contrast material into a contralateral vessel even though the collateral vessel itself might not have been detected on the angiogram (Fig 1)

The left ventriculogram was analyzed grossly for size and for localized or diffuse contraction abnormalities as described by Herman and colleagues[19]

The results of the treadmill exercise ECG the cine left ventriculograms and the pacing ventricular function curves as well as the severity of the angina pectoris and the history for previous myocardial infarction were compared for the two groups of patients and analyzed by chi square analysis

Results

The 78 patients included 67 men and 11 women Forty eight of the 78 (62 per cent) had *coronary collaterals* as defined above visualized during coronary arteriography The mean age of this group was 53 years The severity of their angina pectoris averaged Grade 2 Of the 48 33 (68 per cent) had a history of previous myocardial infarction (Table I)

Thirty eight of the 48 had stress testing 23 had right atrial pacing during the cardiac catheterization and 15 had treadmill exercise ECG s Abnormal pacing ventricular function curves

Table II Comparison of patients with and without collateral vessels

	Collaterals		*No collaterals*	
	No	*%*	*No*	*%*
Single vessel involvement	2	4	2	7
Two vessel involvement	3	6	6	20
Three vessel involvement	43	90	22	73

were obtained in 22 of 23 patients (96 per cent) Twelve of 15 patients (80 per cent) had positive treadmill ECG s

Of the 48 patients 43 (90 per cent) had three vessel disease three had two vessel disease and two had single vessel disease

Forty three of the 48 (90 per cent) patients had contraction abnormalities noted on cine left ventriculography In 16 of the 43 this was localized and in 27 diffuse changes were apparent. No patient had a left ventricular aneurysm mitral valvular insufficiency or a ventricular septal defect

Of the 78 patients 30 (38 per cent) *did not have collateral vessels* visualized during coronary arteriography the mean age was 52 years (see Table I) The severity of angina pectoris in this group also averaged Grade 2 while only eight patients of the 30 (27 per cent) had a history of previous myocardial infarction Twenty six patients of this group had stress testing 15 had atrial pacing and 11 had treadmill exercise ECG s Nine of the 15 (60 per cent) had abnormal pacing ventricular function curves and 10 of 11 patients (91 per cent) had positive treadmill exercise ECG s Twenty two patients of the 30 (73 per cent) had triple vessel disease six had two vessel disease and two had single vessel disease

Sixteen patients of the 30 (53 per cent) had abnormal left ventricles as defined by cine ventriculography including eight with primarily local and eight with diffuse contraction abnormalities

A *comparison* of the two groups disclosed the following The severity of the angina pectoris was Grade 2 in each and the number of positive treadmill exercise ECG s was not statistically

different between those with and those without collaterals However, the group with collateral vessels had a statistically significant greater extent of obstructive coronary disease (P = 0 05) (although there was no difference in the number of patients with two and three vessel disease in the two groups), a higher incidence of previous myocardial infarction (P < 0 01), a greater number of abnormal pacing ventricular function curves (P < 0 01), and more contraction abnormalities on cine left ventriculography (P < 0 025) (Table II)

Discussion

Collateral circulation of the coronary arteries and its functional significance have received considerable attention but the role of these collaterals in patients with coronary heart disease has not been clarified and their importance is still being debated[1 13 29 32] Their presence suggests a protective effect however there has been no consistent evidence in man that these vessels are effective in reducing the symptoms of angina pectoris preventing myocardial infarction or even extending life Also there may be no significant difference between patients with coronary heart disease with and those without collateral circulation in relation to the resting and exercise ECG or ventricular performance

Coronary arteriography during life is an excellent method to visualize collateral blood vessels but unlike the contrast injections of postmortem specimens the radiopaque medium is not forced into the coronary arteries Rather it is mixed with the flow of blood as blood enters the coronary ostium from the aorta Only those vessels within the resolving power of the system (100 micra or more in diameter) and carrying functionally significant flow receive enough contrast agent to become individually detectable in the living heart by current radiographic techniques We must assume that in hearts with normal coronary arteries, the flow through these anastomotic channels is at best minimal and although these coronary collaterals are anatomically present they are functionally insignificant in the normal heart, at least at rest When there is an atherosclerotic obstruction in a major coronary vessel, the pressure beyond the obstruction falls, this generates a gradient of pressure between the proximal and the distal portion of this vessel[8 9 14] Also, a gradient of pressure may be established between another coronary artery and the segment of the diseased artery distal to the obstruction This gradient apparently generates flow across pre existing anastomotic channels and enlarges them Blood flow across the functioning anastomoses sets the stage for opacification by coronary arteriography Gensini and DaCosta[6] demonstrated that the visualization of intra arterial coronary anastomoses is a reliable indirect sign of significant coronary artery involvement They believed that they may account for a normal resting ECG even in patients with major arterial occlusion Since not all patients with severe coronary artery disease have angiographically visible collaterals other presently unknown factors are also presumed to be important in their development.[2 8]

Theoretically collaterals may have a significant protective effect or may at the least significantly influence the course of angina pectoris and acute myocardial infarction, they may also affect characteristics of the ECG at rest and during exercise However, their role is not simple—witness the debate that still continues Some of this uncertainty as to their functional significance may be the result of our criteria for the actual presence of collateral vessels in the living state Only channels larger than 100 micra can be seen although for the purposes of this study we and other investigators as well, have used indirect evidence for their presence, that is the visualization of a coronary artery after contrast injection into a contralateral vessel with no visible communication between the two Also in evaluating the effects of collaterals we are hampered since no reliable method is available to determine regional blood flow We now estimate this on the basis of the flow of contrast material by angiography but this method is crude and we may be missing important differences in patients even when the same apparent degree of collateral vessel formation is grossly evident

On the basis of our criteria for the presence or absence of collaterals vessels and realizing that we are unaware of true regional blood flow our study disclosed the following relationships. In comparing our patients with and those without coronary collateral vessels we found that although the two groups are alike clinically with regard to both the severity of their angina and the frequency of positive (ischemic) responses to

treadmill testing the groups with the collateral vessels had more statistically significant obstructive coronary disease a higher incidence of previous myocardial infarction (clinically and by ECG) more frequent left ventricular contraction abnormalities demonstrated angiographically and poor myocardial function as disclosed by more frequent abnormal pacing ventricular function curves In our experience coronary collateral vessels are associated with more extensive ob tructive coronary disease and impairment of the left ventricle performance yet this group was not clinically different from those without collaterals in the severity of their angina or their ability to exercise Although these patients are disabled, as evidenced by hemodynamic and clinical findings they are alive and functioning at the same level or almost at the same level as patients with less advanced disease There is also an implication that when a severe obstruction occurs in a major coronary vessel, intercoronary or intracoronary collateral development may reduce the extent of myocardial necrosis and/or ischemia and thereby sustain life[33] Obviously we are not in a position to surgically close collateral circulation to determine whether the patient would thereupon die suddenly However we have observed many patients with severe obstructive lesions of all three coronary vessels but with extensive collateral blood supply With regard to these patients there is reason to believe that they are alive and functioning albeit at lower levels because of their extensive collateral blood supply Furthermore we have observed that as to some patients in whom successful bypass is performed to the distal coronary vessel the postoperative coronary arteriogram may demonstrate no collateral blood supply although it was present preoperatively This is similar to a recent animal study[34] This phenomenon suggests that the augmented coronary blood flow through the patent bypass results in less demand for collateral blood flow resulting in an abrupt disappearance of collaterals Our study agrees with the findings of Helfant and associates[4] who showed that there were no significant differences between the two groups in (1) levels of physical activity (2) duration of angina or (3) prevalence of ECG hemodynamic and ventriculographic abnormalities However our patients with collaterals had a greater frequency of prior myocardial infarction Myocardial ischemia was apparently more prevalent in patients *with* than in those *without* collaterals in their study as evidenced by significantly greater frequency of abnormal postexercise ECG s and myocardial lactate production The incidence of positive exercise studies was the same in both of our groups In the experience of Helfant and colleagues[4] the incidence of acute myocardial infarction during the follow up period was nearly identical in the two groups The mortality rate was lower in patients *with* than in those without collateral vessels but this finding did not achieve statistical significance They concluded that although collateral vessels do not necessarily prevent myocardial ischemia or myocardial infarction the mortality rate may be reduced

The general experience regarding the presence and functional significance of coronary collateral vessels may be summarized as follows In 60 to 80 per cent of patients with significant (over 75 per cent) obstructions in at least one coronary artery these potential channels will enlarge and become functional There is a progressive increase in the number of collateral vessels with an increase in the number of coronary arteries obstructed.[28, 5] The presence of collaterals implies myocardial ischemia but in certain patients these vessels fail to develop since other factors may also be important Although collaterals may enhance regional blood flow present studies do not show any contribution to total myocardial blood flow reserve except in the case of certain bridge collaterals[6] Clinically collateral channels generally do not appear to be adequate to meet myocardial oxygen needs during stress since the same degree of angina and as many positive (ischemic) exercise tests are present in those patients with or without these variables Apparently there are limits to the extent that collateral circulation can develop and it is possible that the patient with coronary disease eventually reaches a stage at which more collaterals cannot develop If this is true then the patient who has experienced angina pectoris has ended his ability to expand his collateral circulation at this point one would expect little prognostic significance in either group of patients (with or without collaterals) Presumably the collateral circulation will continue to develop in the patient with advancing and progressive obstructive coronary heart disease When he experiences angina pectoris this symptom is an indication that more

collaterals can no longer develop and then he may become symptomatic Therefore in selecting patients with angina pectoris, there is actually no apparent difference clinically between *those patients with and those without collaterals* so long as they have angina pectoris Another way to look at this problem is to suggest that angina pectoris will develop earlier in a patient without collateral blood supply and with advancing coronary heart disease than in a patient with collateral circulation However collaterals do not protect against myocardial infarction nor against functional abnormalities of the left ventricle as disclosed by angiography and pacing ventricular function curves These patients however may be the most capable of surviving myocardial infarction thereby living longer although their arterial and myocardial disease is more extensive

Summary

To appraise the functional significance of coronary collateral vessels 78 consecutive patients with angina pectoris and at least 75 per cent obstruction in a major coronary vessel were studied clinically hemodynamically and angiographically and by stress testing Forty eight of them (62 per cent) had coronary collateral vessels When patients with collaterals were compared with those without the severity of angina pectoris and the number of positive treadmill ECG's were not statistically different The patients with collaterals had a greater incidence of past myocardial infarction 33/18 (68 per cent) vs 8/30 (27 per cent) ($P = 0.001$) more extensive obstructive disease angiographically 8.0 ± 0.4 vs 6.3 ± 0.5 ($P = 0.05$) more abnormal pacing ventricular function curves 22/23 (96 per cent) vs 9/15 (60 per cent) ($P = 0.01$) and a greater incidence of left ventricular contraction abnormalities 43/48 (90 per cent) vs 16/30 (53 per cent) ($P = 0.025$)

Patients who have coronary artery disease and collateral vessels cannot be distinguished from their counterparts without collaterals on a clinical basis except for a greater incidence of myocardial infarction in the former Present evidence implies that collateral vessels may protect the patient by delaying the onset of angina pectoris but when angina occurs these patients have more extensive coronary artery disease and greater myocardial dysfunction In addition collaterals although not preventing, may limit the extent of myocardial infarction and reduce immediate mortality The prognosis *from the onset of angina pectoris* may be worse in those patients with collateral vessels however, because of their more extensive disease

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Assessment of aortocoronary saphenous vein bypass function utilizing selective indicator dilution curves

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Various methods have been utilized for the postoperative evaluation of aortocoronary saphenous bypass graft function in man Roentgen videodensitometry [1,2] hydrogen perfusion,[3,4] rubidium coincidence counting,[5] and xenon clearance[6] techniques have been applied for the study of such grafts, providing objective data regarding bypass blood flow

We describe here the use of selective graft dye dilution curves as a method for assessing aortocoronary bypass function

Material and methods

Twenty one subjects comprised the study group There were 20 men and one woman whose ages ranged from 38 to 68 years with a mean of 54 years All patients underwent aortocoronary saphenous vein bypass graft implantation[7] for angina pectoris secondary to angiographically demonstrable coronary artery disease The anatomic sites of the bypass graft implants were as follows 8 subjects—isolated right coronary artery, 12 subjects—combined right and left anterior descending coronary artery, and 1 patient—combined right left anterior descending and circumflex bypass grafts No subject had a Y" graft This provided a total of 35 grafts for study After a postoperative period ranging from one to 13 months each subject underwent right and left heart catheterization selective graft cineangiography, and indicator dilution study All studies were performed in the catheterization laboratory with patients in the non sedated post absorptive state in the supine position Utilizing 1 per cent lidocaine anesthesia an antecubital fossa incision was made The right or left brachial artery and a medial antecubital vein were isolated and incised A No 7½ Sones Positrol catheter was introduced into the artery and was advanced to the ascending aorta A No 8 Zucker biopolar catheter was introduced into the vein and was advanced to the pulmonary artery In most cases the orifice of the aortocoronary graft was identified by metallic surgical clips which had been affixed to the aorta near the origin of the graft during the operation The right, left anterior descending or left circumflex grafts were selectively catheterized and 4 to 8 ml of 75 per cent Hypaque (sodium and meglumine Diatrizoates) was introduced by hand injected syringe The method utilized for positioning of the catheter was similar to that used for selective coronary arteriography[8] Cineangiograms were obtained using a Siemens 6 inch/9 inch image intensifier and a 35 mm Arriflex camera operated at a speed of 32 frames per second In addition sequential 14 by 14 inch roentgenograms of graft opacification were obtained at a speed of six exposures per second utilizing a Schonander rapid changer Angiograms were taken in multiple projections including the left anterior oblique position at about 75 degrees and the right anterior oblique position at 50 degrees In all cases selective left and right coronary cineangiography of the bypassed artery was performed in a

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similar manner Two observers independently assessed the graft and coronary angiograms with respect to (1) patency of the graft and of the proximal segment of the bypassed coronary artery (2) degree of clearance of radiopaque medium from the graft or bypassed coronary artery (assigning good or poor flow to each) and (3) a comparison of the rate of opaque dye clearance in the graft and bypassed coronary artery No subject had tricuspid or pulmonic insufficiency In general graft or coronary artery flow was considered poor if the opaque medium was not cleared from the vessel after four cardiac cycles

Dye dilution curves After the graft and coronary angiograms were obtained the Sones catheter was repositioned at (1) the ascending aorta just above the orgin of the grafts (2) the orifice of each graft and (3) in 16 instances the ostium of either the right or left coronary artery which had been bypassed. The method for obtaining aortic selective coronary and bypass graft dye dilution curves in this study was similar to that previously described for coronary arteries in normal subjects and patients with coronary disease [9] After confirmation of the catheter tip location by a small injection of Hypaque blood was withdrawn from the main pulmonary artery through the Zucker catheter at a speed of 38 2 ml per minute Cardiogreen indicator (indocyanine green 3 1 mg) was injected by hand using a precalibrated dye dilution tube attached to a syringe containing 5 ml of 5 per cent dextrose in water The time of injection was carefully recorded and as soon as the indicator injection was completed, the catheter tip was quickly withdrawn under fluoroscopic control from the ostium of either the graft or the coronary artery This latter maneuver was performed in order to prevent possible obstruction to graft or coronary flow by the catheter Continuous sampling of main pulmonary artery blood was accomplished by means of a Gilford cuvette densitometer (Model 103 IR) A 30 cm long plastic tubing (volume—4 ml) connected the sampling catheter to the dye dilution cuvette The sampling delay through the catheter tubing was determined to be four seconds Thus for each patient a minimum of two dye dilution curves were obtained, the first from aortic injection and the second from graft injection In 16 cases injection into the ostium of the bypassed coronary artery accounted for a third dye dilution curve In those patients with more than one graft, a similar set of curves was obtained from injection of the second graft and bypassed coronary artery Lead II of the electrocardiogram was recorded simultaneously with the selective dye dilution curves in an Electronics for Medicine DR 12 oscilloscopic photographic recorder at a paper speed of 5 mm per second The aortic graft and coronary artery dye dilution curves were then replotted on semilogarithmic paper and the following measurements were obtained (1) corrected appearance time (AT) (appearance time minus four seconds delay) (2) build up time (BT) (3) peak amplitude (PA) (4) peak amplitude divided by buildup time (PA/BT) [9] (5) clearance time (CT) and (6) spread ratio (SR) [9,10] Further more dye dilution curves were studied for contour abnormalities including notches slurrings, and double peaks. The results of independent angiographic evaluation of coronary artery and graft flow were then compared with the dye dilution curve measurements

Statistical significance of the differences between mean values was performed using the Student t test

Results

Angiographic evaluation Twenty eight of 35 (80 per cent) grafts were patent. The distribution of graft patency by anatomic location of coronary artery was 17/21—right coronary artery 10/13—left anterior descending coronary artery and 1/1—left circumflex coronary artery Fifteen of 28 grafts were judged as having good flow and 13/28 as showing poor clearance of the angiographic medium. Four patent grafts were stenosed by 50 to 80 per cent of the lumen diameter The bypassed segments of 8 right 7 left anterior descending and 1 circumflex coronary arteries were opacified by selective coronary arteriography

The rate of clearance of opaque medium was judged as greater in the graft than in the bypassed coronary artery in four cases greater in the bypassed coronary artery than in the graft in four cases and equal in both the graft and the bypassed coronary artery in eight instances

Selective dye dilution curves Graft injection with Cardiogreen did not result in disturbances of rate rhythm or conduction in the electrocar

Table I Mean (± 1 standard deviation) values of measurements from dye dilution curves obtained by injection into the aorta, patent or occluded graft and sampling in the main pulmonary artery The significance of the difference between various mean values is indicated (P)

		Appearance time (AT sec.)	*Build up time (BT sec.)*
A	Aorta (AO) vs occluded (OCC) graft	AO = 13 3 ± 2 5 OCC = 13 7 ± 2 8 P > 0 7	AO = 7 2 ± 2 0 OCC = 8 3 ± 3 1 P > 0 2
B	Aorta (AO) vs patent graft (PAT)	AO = 13 3 ± 2 5 PAT = 8 1 ± 2 2 P < 0 001	AO = 7 2 ± 2 0 PAT = 6 1 ± 2 0 P > 0 05
C	Patent (PAT) vs. occluded (OCC) grafts	PAT = 8 1 ± 2 2 OCC = 13 7 ± 2 8 P < 0 001	PAT = 6 1 ± 2 0 OCC = 8 3 ± 3 1 P < 0 05
D	Angiographic evaluation of graft flow Good vs poor	Good = 7 6 ± 1 9 Poor = 8 8 ± 2 4 P > 0 1	Good = 5 2 ± 1.2 Poor = 7 1 ± 2 3 P < 0 01

Table II Mean (±1 standard deviation) values of measurements from dye dilution curves obtained by injection into grafts and the ostia of coronary arteries which had been bypassed The significance of the difference between mean values is indicated (P)

		Appearance time (AT sec)	*Build up time (BT sec.)*
A	Graft flow greater than bypassed coronary flow	GFT = 7 3 ± 2 3 COR = 8 3 ± 2 8 P > 0 5	GFT = 4 9 ± 1 0 COR = 7 9 ± 1 9 P < 0 05
B	Bypassed coronary flow greater than graft flow	GFT = 6 9 ± 1 5 COR = 6 6 ± 1 9 P > 0 8	GFT = 6 8 ± 1 0 COR = 5 4 ± 0 5 P < 0 05
C	Graft flow equal to bypassed coronary flow	GFT = 8 8 ± 1 7 COR = 9 1 ± 2 2 P > 0 7	GFT = 6 8 ± 3 1 COR = 6 6 ± 1 9 P > 0 8

diogram although in several cases minor T wave and S T segment changes were observed There were no significant differences between the mean values for appearance time build up time peak amplitude PA/BT ratio clearance time and spread ratio obtained from selective right and left aortocoronary graft injection Similarly, there were no significant differences between aortic root and occluded graft dye curve measurements (Table I A) There were highly significant differences (P < 0 001) between mean group measurements for appearance time peak amplitude and PA/BT ratio when aortic and patent graft dye curves were compared The patent graft mean appearance time was shorter (8 1 ± 2 2 vs 13 3 ± 2 5 seconds) mean peak amplitude higher (51 0 ± 20 5 vs 29 9 ± 11 0 ml) and mean PA/BT greater (9 6 ± 5 3 vs 4 4 ± 2 4) Patent graft clearance times were shorter (39 6 ± 10 0 vs 46 3 ± 11 7 seconds) and spread ratio greater (3 4 ± 0 9 vs 2 7 ± 0 7) Furthermore there were uniformly earlier ap

Peak amplitude (PA mm.)	*PA/BT*	*Clearance time (CT sec)*	*Spread ratio (SR)*
AO = 29 9 ± 11 0 OCC = 31 6 ± 8 9 P > 0 7	AO = 4 4 ± 2 4 OCC = 4 6 ± 2 2 P > 0 8	AO = 46 3 ± 11 7 OCC = 41 7 ± 12 7 P > 0 3	AO = 2 7 ± 0 7 OCC = 2 3 ± 0 8 P > 0 3
AO = 29 9 ± 11 0 PAT = 51 0 ± 20 5 P < 0 001	AO = 4 4 ± 2 4 PAT = 9 6 ± 5 3 P < 0 001	AO = 46 3 ± 11 7 PAT = 39 6 ± 10 0 P < 0 05	AO = 2 7 ± 0 7 PAT = 3 4 ± 0 9 P < 0 01
PAT = 51 0 ± 20 5 OCC = 31 6 ± 8 9 P < 0 05	PAT = 9 6 ± 5 3 OCC = 4 6 ± 2 2 P < 0 05	PAT = 39 6 ± 10 0 OCC = 41 7 ± 12 7 P > 0 6	PAT = 3 4 ± 0 9 OCC = 2 3 ± 0 8 P < 0 02
Good = 62 0 ± 21 1 Poor = 38.3 ± 10 1 P < 0 01	Good = 12 9 ± 5 0 Poor = 5 6 ± 1 8 P < 0 001	Good = 35 9 ± 7 6 Poor = 43 9 ± 11 1 P < 0 05	Good = 3 1 ± 1 0 Poor = 3 7 ± 0 8 P > 0 1

Peak amplitude (PA mm.)	*PA/BT*	*Clearance time (CT sec)*	*Spread ratio*
GFT = 67 ± 12 9 COR = 36 5 ± 3 4 P < 0 01	GFT = 14 5 ± 5 4 COR = 4 9 ± 1 4 P < 0 02	GFT = 33 5 ± 8 3 COR = 45 ± 7 4 P > 0 05	GFT = 2 9 ± 0 4 COR = 4 1 ± 2 1 P > 0 3
GFT = 44 ± 9 5 COR = 90 ± 30 3 P < 0 05	GFT = 6 5 ± 2 1 COR = 16 6 ± 4 8 P < 0 01	GFT = 39 5 ± 6 2 COR = 36 3 ± 15 0 P > 0 7	GFT = 3 9 ± 0 8 COR = 3 4 ± 1 3 P > 0 5
GFT = 53 1 ± 24 7 COR = 56 8 ± 29 9 P > 0 7	GFT = 9 4 ± 6 6 COR = 9 5 ± 5 7 P > 0 9	GFT = 42 4 ± 12 9 COR = 45 3 ± 13 0 P > 0 6	GFT = 3 2 ± 0 9 COR = 3 5 ± 1 5 P > 0 6

pearance times greater PA/BT ratios larger spread ratios and shorter clearance times when patent graft dye curves were compared with aortic dye curves in individual subjects There were no significant differences between aortic and patent graft build up times (Table I B) Typical dye curves obtained from aortic and patent graft injection are shown in Fig 1 There were highly significant differences between the patent and occluded graft mean appearance times (8 1 ± 2 2 seconds vs. 13 7 ± 2 8 seconds P < 0 001 Fig 2)

Differences between mean build up times peak amplitudes PA/BT ratios and spread ratios were also significant but there was overlap of individual values (Table I C) When PA/BT ratios of dye dilution curves obtained from injection of grafts with angiographic evidence of good and poor flow were compared (Table I D) significant differences were noted (12 9 ± 5 0 vs. 5 6 ± 1 8 P < 0 001 Fig 3) Thus the greater PA/BT ratio overlap observed when patent and occluded graft values were compared can be attributed to

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D	Angiographic evaluation of graft flow Good vs poor	Good = 7 6 ± 1 9 Poor = 8 8 ± 2 4 P > 0 1	Good = 5 2 ± 1 2 Poor = 7 1 ± 2 3 P < 0 01

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evaluating bypass graft flow It is noteworthy that there was a correlation of certain dye curve measurements with the degree of flow in both saphenous grafts and bypassed coronary arteries as determined by selective graft and coronary arteriography Examination of the mean group data from different selective dye injection sites reveals that in every case there were significant variations of the peak amplitude/build up time ratios where such differences might be expected. This ratio is apparently the most discriminating measurement because it accounts for dye dispersion and rate of dye particle detection in a single calculation

Although the selective dye dilution method is qualitatively satisfactory for assessing graft flow there are certain limitations inherent in the technique Since dye sampling is done in the main pulmonary artery the curves may be influenced by either systemic venous return or tricuspid and pulmonic valvular regurgitation Despite these drawbacks of the technique it is clear that the dye dilution curves do in part represent flow of the indicator through the grafts coronary arteries and coronary venous system

Injection of indocyanine green into patent grafts with satisfactory clearance of contrast medium resulted in dye dilution curves which had higher peak amplitudes shorter build up times, and greater peak amplitude/build up time ratios than did selective injection into the aorta, obstructed grafts and grafts with slow clearance of angiographic medium Furthermore there were abnormal contours in curves obtained from injection of grafts with stenosis and slow opaque medium clearance

Factors which probably influence the clearance of angiographic medium and the contour of dye dilution curves include the degree of graft patency anatomic state of the distal coronary arterial "run off" system graft and coronary arterial resistance the extent of distal coronary collateral circulation cardiac output and blood viscosity The relative importance of each of the above variables in the genesis of characteristic dye curves described here is currently unknown and awaits future investigation The theoretical merit and disadvantage of coronary sinus sampling during injection of indocyanine green into the coronary arterial system have been previously discussed.[9] Coronary sinus sampling does not appear to have any practical advantage over the method described here

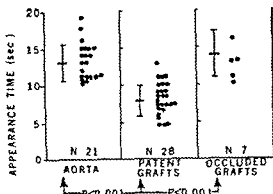


Fig 2 Appearance times measured from aortic patent graft and occluded graft dye dilution curves The mean values ± one standard deviation are indicated. There are highly significant differences between the dye curve measurements for patent grafts when compared with those from aortic and occluded graft injection.

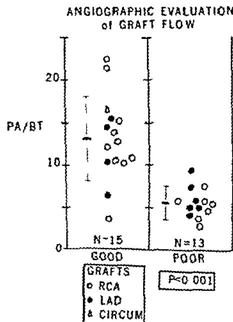


Fig 3 Values for peak amplitude/build up time ratios from dye curves obtained by injection into grafts with "good" and "poor" angiographic flow The mean values ± one standard deviation are indicated. There are significant differences between the mean values for the two groups (*RCA LAD circum.* = right, left anterior descending and left circumflex aortocoronary grafts respectively)

Advantages of the technique Equipment for selective dye dilution study is readily available in most laboratories where cardiac output and shunt calculations are performed We have not observed any untoward arrhythmia depression

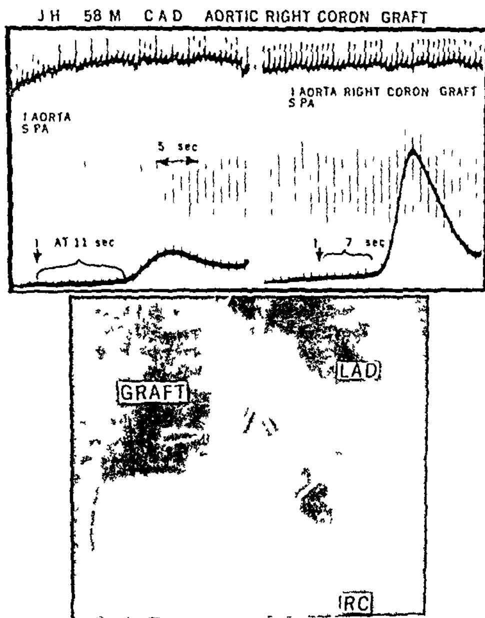


Fig 1 *Upper panel*, Lead II of the electrocardiogram and selective dye dilution curves obtained from injection (I) into the aorta and patent right aortocoronary graft with sampling (S) in the main pulmonary artery of a 58 year old man with coronary artery disease Note the shorter appearence time (AT) faster inscription of the ascending limb and higher peak concentration of the graft dye dilution curve when compared with the aortic curve *Lower panel*, Angiographic appearance of the right coronary graft Note retrograde filling of the left anterior descending (*LAD*) coronary artery via collateral vessels from the distal right coronary (*RC*) artery

the low PA/BT ratios measured in patients with patent grafts and poor flow Indicator injection of 10/13 grafts with stenosis or poor clearance of angiographic medium resulted in abnormal dye curve contours including 'double humps' (Fig 4) When coronary arterial flow appeared more satisfactory than bypass graft flow on the angiograms the coronary dye curve build up times were shorter, peak amplitudes higher and PA/BT ratios greater than corresponding measurements from graft dye curves (Table II B) In those cases where graft flow appeared more satisfactory than coronary flow, corresponding differences in these measurements were seen (Table II A and Fig 5) When graft flow was judged as being equal to coronary flow, there were no significant differences between any of the dye curve parameters (Table II C) There was no overlap of individual PA/BT values when the quality of flow in the grafts and coronary arteries was noted (Fig 6) When dye curves from coronary arteries with 100 per cent obstruction were compared with those from the aorta there were no significant differences in any measurement.

Discussion

The selective dye *dilution technique* appears to be a useful adjunct to graft angiography for

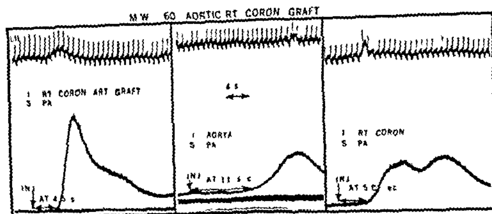


Fig 5 Lead II of the electrocardiogram (L II) and selective dye dilution curves obtained from injection (I) of the right aortocoronary bypass graft aorta and right (rt) coronary artery with sampling (S) in the main pulmonary artery (PA) of a 60 year-old man with coronary artery disease Angiograms demonstrated good flow in the patent right graft and poor flow with 80 per cent obstruction of the right coronary artery The right graft dye dilution curve has a more rapid upstroke and greater peak amplitude than corresponding measurements in the right coronary artery curve Note the double hump configuration of the right coronary artery dye curve

Summary

Aortocoronary saphenous graft function was evaluated in 21 postoperative patients with the selective indocyanine green indicator dilution method. Selective indicator injections were made into the aortic root diseased coronary artery and saphenous bypass graft with constant sampling at the main pulmonary artery There were no major electrocardiographic alterations associated with dye injection Graft aortic and coronary dilution curves obtained from such testing were analyzed with respect to corrected appearance time (AT) build up time (BT) peak amplitude (PA) peak amplitude build up time ratio (PA/BT) clearance time (CT) and spread ratio (SR) When compared with aortic root indicator dilution curves characteristic findings were (1) patent grafts shorter AT ($P<0.001$) higher PA ($P<0.001$) greater PA/BT ($P<0.001$) shorter CT ($P<0.05$) and greater SR ($P<0.01$) (2) occluded graft no significant difference in any measurement There were significant differences in BT ($P<0.01$) PA ($P<0.01$) PA/BT ($P<0.001$) and CT ($P<0.05$) when curves from injection of grafts with good and poor angiographic clearance were compared. Where graft flow appeared more satisfactory than bypassed coronary arterial flow there were significant differences between the majority of these measurements

It is concluded that the selective indicator dilution technique is safe and useful for the evaluation of aortocoronary graft function

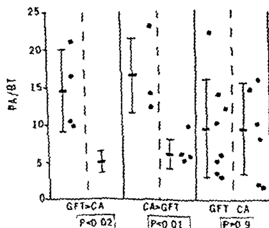


Fig 6 Values for peak amplitude build up time ratios (PA/BT) in those subjects whose angiographic evaluation demonstrated graft flow greater than bypassed coronary artery flow (GFT > CA) bypassed coronary flow greater than graft flow (CA > GFT) and graft flow equal to bypassed coronary flow (GFT = CA) The mean values for PA/BT ± one standard deviation are indicated There are significant differences between the measurements when opaque dye clearance in the grafts and bypassed coronary arteries is unequal

We wish to acknowledge the technical assistance of Nancy Copeland R.N. Carole Crevier Larry Kunger Sydney Peebles Sharon Squire and Les Zendle

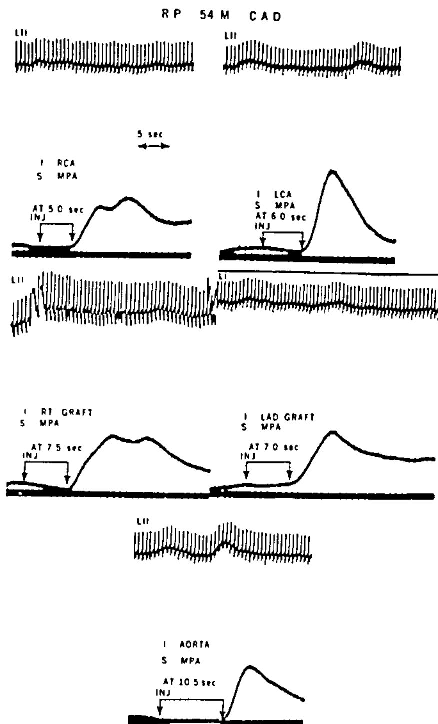


Fig 4 Lead II of the electrocardiogram (*L II*) and dye dilution curves from injection (*I*) of the right coronary artery (*RCA*) left coronary artery (*LCA*) right coronary artery graft left anterior descending (*LAD*) coronary artery graft and aorta with sampling (*S*) in the main pulmonary artery (*MPA*) of a 54 year old man with coronary artery disease The right coronary artery and right aortocoronary graft were obstructed by over 75 per cent of their lumen diameter and demonstrated poor clearance of the angiographic medium Note the double hump configuration of selective dye dilution curves from those respective vessels

of ventricular function or hypotension associated with this technique The selective dye dilution method can be utilized for the postoperative evaluation of patients with aortocoronary grafts and aid in the correlation of clinical response and graft function However the dye dilution techniques outlined herein are not substitutes but supplements to selective angiography in studying patency of and flow through grafts and bypassed coronary arteries Insofar as the dye dilution curves represent flow through the grafts the technique also provides measurable parameters which can be compared if serial graft assessment is undertaken

Case reports

Congenital obstruction of the pulmonary veins at their atrial junctions

Review of the literature and a case report

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Stenosis or atresia of the pulmonary veins with normal connections to the left atrium is a very rare condition and only twelve cases have been described.[1-10] In none of them was the correct diagnosis revealed until at autopsy. The youngest patient was 9 months and the oldest was 11 years of age at death.

Usually several veins were involved and stenosis and atresias could be found in the same patient. In two cases was only one vein involved but this constituted a common trunk to the venous drainage of the whole ipsilateral lung.

Seven patients also had other malformations of the heart and great vessels—i.e., persistent ductus arteriosus, atrial septal defect (two cases), persistent ostium atrioventriculare commune, transposition of the great vessels plus single ventricle plus tricuspid atresia, atrial septal defect plus mitral atresia plus outflow from the right atrium to both ventricles, and, finally, Fallot's anomaly.

The stenotic and atretic segments were localized at the venoatrial junctions. The stenosis was 1 to 2 mm. long but nearly 1 cm. long in one case. The extrinsic diameter of the stenotic segments of the veins was normal or slightly reduced. Microscopic examination disclosed a varying construction of the stenosis. In some cases the stenosis consisted of locally thickened endocardium which encroached upon the mouths of the veins. In the case reported by Contis and colleagues[3] three veins had been stenosed in this way and two of these had been occluded by a thrombosis. In the other cases the stenoses were caused by hypertrophy of the smooth muscles of the media or by non-specific thickening of the intima or changes in both intima and media.

In the pulmonary arteries and veins there were more or less pronounced changes in the intima and media caused by pulmonary arterial and venous hypertension. Small arteriosclerotic plaques were also found in the arteries. The wall of the pulmonary artery was thickened, the elastic fibrils were long and regular as they are in the aorta and also in the pulmonary artery during the fetal and neonatal stages.

In all cases reported there were changes in the pulmonary parenchyma—i.e., emphysema, interstitial fibrosis, hemorrhages and hemosiderosis. Sometimes the pulmonary changes were localized only in the lung where venous drainage was rendered difficult, but sometimes also in the other lung. In several cases dilated bronchial and intercostal veins were seen as well as dilated subpleural and mediastinal veins and dilated lymphatic vessels.

The most common symptoms were failure to thrive and gain in weight, fatigue, dyspnea, recurrent respiratory tract infections, hemoptysis and slight cyanosis. Some of the children without other cardiovascular malformations were free from symptoms during the first five years of life while others displayed symptoms during the first half year.

In cases without other heart malformations roentgenographic examination of the chest dis

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Discussion

In all cases reported the elastic tissue of the pulmonary artery had a fetal appearance in dicating that the pulmonary hypertension had developed during the first six months of life [11,13] For this reason and because there often are con comitant cardiovascular malformations and no inflammatory changes in or around the involved venous segments the stenosis and atresias of the pulmonary veins have been considered to be con genital malformations The absence of persis tent fetal venous drainage need not speak against this theory these formations may already have regressed before the development of the occluding changes in the pulmonary veins [4]

Furthermore during fetal life only about one tenth of the output of the right ventricle reaches the lungs [14] and the hemodynamic effect of the partial obstruction to the venous drainage may not be enough to stimulate preservation of the embryological venous drainage After delivery an increasing blood volume reaches the lungs and the effect of the stenosis and atresias is further accentuated by a heart malformation with a left to right shunt.

Except in one case [4] atresias always occured to gether with stenosis In our case the atresia con sisted at least partly of a tissue which was centrally rich in vessels—probably an organized thrombosis as in the case of Contis and associ ates.[3] The under development of the pulmonary artery on the same side as the venous occlusions present in our case has not been observed earlier

Recently Binet and co workers[15] reported stenosis of a solitary right sided pulmonary vein in the hilar region in a girl aged 3½ years, with recurrent hemophysis. Pulmonary venous stasis was observed at chest examination but despite this and despite the symptoms there was only a slight pulmonary hypertension and no hypertro phy of the right ventricle was noted at ECG On the left side the PCW pressure was normal but on the right side it was increased which allowed the authors to suggest the correct diagnosis A successful operative correction was performed.

Stenosis atresias of the pulmonary veins may be assessible to surgical treatment by resection of the stenotic part of the vein or (partial) lung resection if not combined with other too complex malformations Unfortunately it has proved to be difficult to make the correct diagnosis in vivo Coexisting cardiovascular malformations make diagnosis difficult. Obstruction to the pulmonary venous return usually caused atypical symptoms—often wrongly interpreted as caused by infection of the upper respiratory tract The heart murmurs are uncharacteristic Electrocar diogram usually reveals hypertrophy of the right ventricle but not necessarily [15] It is of utmost importance to note the discrete diffuse changes caused by pulmonary venous stasis. Combined with a left atrium of normal size venous stasis speaks in favor of venous obstruction proximal to the atrium Pressure recording with estima tion of the PCW pressure bilaterally and of the pressure in the left atrium is of the greatest diagnostic value Any difference between these two pressures in a child exists only in pulmonary venous obstruction cortriatriatum obstructing atrial tumor and obstructed anomalous pulmo nary venous drainage All of these diagnoses ex cept the first one can be demonstrated or ex cluded by angiocardiography Only in the case of Contis and associates[3] were the circumstances favorable enough to demonstrate the stenosis at the venoatrial junctions In other cases includ ing ours the density of the contrast medium was too low to visualize a short stenosis or atresia hidden behind the left atrium but slow passage of the contrast medium through the obstructed



Fig 3 Angiocardiography with contrast injection into the right ventricle The arteries on the right side are wide There is a slight under development of the left pulmonary artery



Fig 1 June 19 1967 Girl patient aged five months The heart has normal size and volume On the left side the pulmonary arteries are narrow but on the right side they are dilated No stasis of the veins can be seen



Fig 2 Five months later There is slight enlargement of the right ventricle and atrium Slight vascular changes have appeared probably caused by pulmonary venous stasis (also parenchymatous changes in the middle lobe)

closed enlargement of the right ventricle and dilated main stem of the pulmonary artery The lung vessels were described as diffuse accentuated or "increased" and in one case the widths of the vessels were said to be increased centrally but reduced peripherally

At angiocardiography slow passage of the contrast medium through the veins has been noticed by some authors In one case only the stenosis of the pulmonary veins could be seen at angiocardiography at re examination [10]

Pressure recordings showed constant pulmonary hypertension In one case the PCW pressure was recorded as well as the pressure in the left atrium which were 16 and 2 mm Hg respectively [3] The two pressures however, were observed at two different examinations with an interval of two or three months

Case report

Girl born after uncomplicated pregnancy Feeding difficulties and repeated upper respiratory tract infections during her first months of life At 10 months of age symptoms of right heart failure developed. An uncharacteristic heart murmur was heard, and ECG demonstrated enlargement of the right atrium and hypertrophy of the right ventricle

Roentgenographic examination showed a normal heart but the pulmonary arteries were wide in the right lung but narrow in the left lung (Fig 1) At a later examination the right side of the heart was slightly enlarged and pulmonary venous stasis appeared (Fig 2) Finally parenchymatous changes probably caused by pulmonary hemorrhages, were seen

At heart catheterization at the age of 10 months, the systolic pressure in the right ventricle and pulmonary artery was 55 and 45 mm Hg respectively The catheter could pass from the right to the left atrium the pressure in the latter being 2 mm Hg No PCW pressure recording was obtained. Blood oxygen analyses demonstrated a left to right shunt through an atrial septal defect and the relation between the pulmonary and the systemic flow was 2 1

Angiocardiography showed wide branches of the right pulmonary artery but the left pulmonary artery and its branches were poorly developed (Fig 3) The veins from the right lung emptied into the left atrium in ordinary time The circulation through the left lung was very slow and still 6 5 seconds after the contrast injection contrast medium was to be seen in the arteries but not in the veins

Autopsy findings

There was pronounced hypertrophy of the wall of the right ventricle and an atrial septal defect with a diameter of 6 mm The mouths of all four pulmonary veins could be identified in the wall of the left atrium The right pulmonary veins were normal The outer diameter of the two left pulmonary veins was reduced In the lungs there were fibrosis and hemorrhages of varying age The subpleural veins were dilated

Microscopic examination The elastic fibrils of the pulmonary artery were long and regular (fetal appearance) The intima and media in the small arteries and veins were thickened and some arteriosclerotic plaques and thrombosis of varying age were found All the changes were more pronounced on the left side In the two left pulmonary veins all the wall layers were thickened and the intima thickness was increased toward the left atrium At the atrial junction there was a 5 to 6 mm long occlusion of the two veins, which near the atrium consisted of fibrotic tissue rich in vessels and of a thrombosis distally It could not be determined whether these changes partly consisted of a primary atresia or whether the total occlusion was caused by thrombosis in a stenotic segment

Alternating Type A and Type B Wolff Parkinson-White syndrome

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The Wolff Parkinson White syndrome as originally described consisted of electrocardiographic changes of a short P R interval initial slurring of the QRS due to a delta wave and wide QRS occurring in young adults prone to the development of supraventricular tachycardias[1] The electrocardiographic changes may be divided into two types depending on the direction of the delta wave vector in Type A the vector is anterior and in Type B posterior[2-4] The remainder of the QRS complex represents 0 to 100 per cent fusion between anomalous pathway conduction and conduction that utilizes the normal atrioventricular conduction system[5-11] Although the existence of more than one accessory pathway has been suggested[12] and has actually been documented in a monkey[13] this phenomenon has not been convincingly documented in man We are reporting a case of a patient with alternating W P W Type A and Type B

Case report

D G is a 54 year-old man with a six year history of palpitations associated with chest discomfort There was no history of shortness of breath paroxysmal nocturnal dyspnea angina pectoris hypertension diabetes or thyroid disease He was sent to the United States Public Health Service Hospital in September 1971 for further evaluation.

Physical examination was within normal limits The ECG revealed W P W Type A without arrhythmias He was

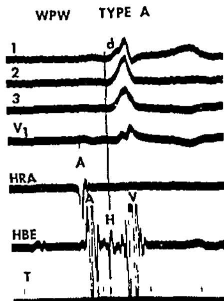


Fig 1 His bundle electrogram W P W Type A From top to bottom are standard ECG Leads I II III and V_1 high right atrial electrogram *(HRA)* *His bundle electrogram (HBE)* and time lines *(T)* Subsequent figures are similarly labeled. The delta wave is most apparent in Lead I It is readily seen that the onset of the delta wave occurs at approximately the same time that the His bundle is depolarized.

brought to the catheterization laboratory in the non sedated postabsorptive state after informed consent was obtained. A His bundle electrogram was obtained as previously described.[14] In addition, a quadripolar electrode catheter was percutaneously introduced into a basilic vein and fluoroscopically positioned against the lateral wall of the high right atrium The proximal pair of electrodes recorded a high atrial electrogram while the distal pair was utilized for atrial pacing

His bundle recordings demonstrated typical W P W Type A (Fig 1) Atrial echoes and supraventricular tachycardia were readily initiated and were terminated by appropriately timed atrial depolarizations These echoes and tachycardia *only occurred if the premature atrial beat were conducted*

F om th Ca d pulmo ry Labo atory U ted State Publ c Health Servi Hosp tal, Staten I l nd, N Y

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pulmonary veins has been reported in several cases

Centrally located stenosis of the pulmonary veins appears to be easily demonstrated at angiocardiography [15,16] Venous occlusion caused by sclerosing mediastinitis[17] or widespread obstructive lesions of small pulmonary veins[18,19] are probably impossible to diagnose pre operatively

Summary

A survey of the reports of congenital stenosis and/or atresias of the pulmonary veins is pre sented and a new case added. The correct diag nosis has not been made in vivo Recurrent respiratory tract infections' and hemoptysis are the most common symptoms Pulmonary venous stasis seen at the chest examination difference in the pressure of the left atrium and the PCW pressure in either or both lungs and slow passage of the contrast medium through the obstructed vein may suggest the diagnosis Angiocardiography can also exclude other condi tions which may cause the same symptoms

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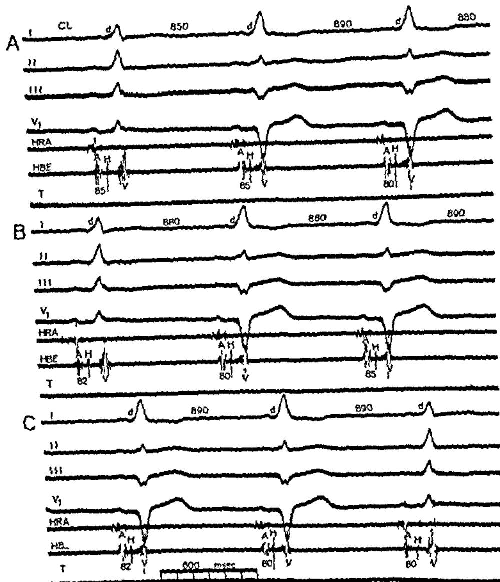


Fig 3 A through C Intermittent W P W Types A and B This is a continuous tracing The first beat is W P W Type A however in the next two beats the delta wave and QRS change to a W P W Type B This change in Type A and B continued unrelated to sinus rate or A V nodal conduction time (A H interval) The onset of the delta wave occurred at the same time or just after the His bundle deflection in both types of W P W complexes and never approached the 50 msec H V interval of the normal beat of Fig 2

The supraventricular tachycardias seen in this syndrome can involve the accessory pathway with antegrade conduction down the normal atrioventricular conduction system and retrograde conduction to the atrium via the accessory pathway in a reciprocal rhythm [6,7,16] Our patient demonstrated a supraventricular tachycardia that was easily induced while he demonstrated Type A configuration It is possible that under different circumstances the β bypass may have been utilized during his tachycardias Although surgical ablation of the accessory pathway has been successfully utilized in the management of refractory arrhythmias in patients with W P W Type B [8,11,17] the more variable location of the bypass tract in W P W Type A usually prevents successful surgery [5] Thus in a patient who demonstrates utilization of either pathway surgical ablation is probably not indicated. Even if one could surgically produce A V block [18,19] and ablate the Type B pathway the patient would still be at risk for the development of supra

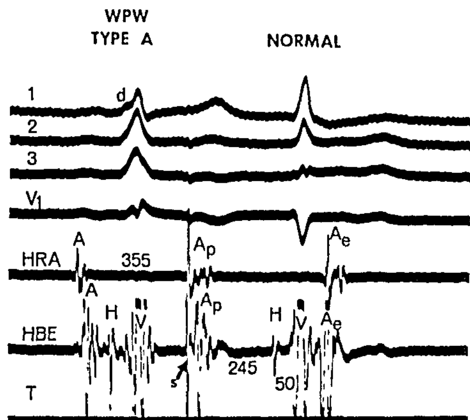


Fig 2 Production of an atrial echo following a premature atrial depolarization The first beat is typical W P W Type A and is followed by a stimulated premature atrial depolarization at a coupling interval of 355 msec The premature atrial beat is antegradely blocked in the accessory pathway and conducts to the ventricle solely by his normal atrioventricular conducting system with an A H of 245 and an H V of 50 msec Ventricular depolarization is followed by an atrial echo (low to high sequence) which conducts retrogradely up the now recovered accessory pathway Note the premature atrial beat results in a normal QRS complex 70 msec in duration with a small q wave in Lead I and small r wave in V_1

entirely by the normal atrioventricular conducting system the atrial echo resulting from retrograde utilization of the accessory pathway (Fig 2)

The patient was discharged on quinidine sulfate 300 mg every 6 hours and remained asymptomatic Two months later he volunteered for another catheterization to investi gate the effect of quinidine on his accessory pathway His physical examination was again unremarkable

The procedure was performed as described above During the study he intermittently developed Type B W P W alter nating with Type A (Fig 3) No atrial echoes or supra ventricular tachycardia could be precipitated by atrial stimulation At the termination of the procedure he reverted to stable Type A W P W He has remained asymptomatic on quinidine Unfortunately we were not able to obtain vector cardiograms during cardiac catheterization when the episode alternating of Type A to Type B W P W occurred

Discussion

The two basic types of W P W complexes cor relate with the location of the accessory path way in Type A it lies posteriorly within or to the right or left of the intraventricular septum and in Type B it is located anterolaterally in the right ventricle near the atrioventricular groove [5,11] Our patient had electrocardiographic evidence of antegrade conduction utilizing both bypass tracts Ramachandran[15] reported a case with alleged Type A and B conduction but careful scrutiny of the electrocardiograms pre sented demonstrated that what was labeled Type B conduction had a positive delta wave vec tor not only in V_1 but throughout the precordial leads In addition the QRS in V_2 was positive Thus this case does not fulfill the criteria of Rosenbaum and colleagues [12] Therefore one might conclude that what was labeled 'Type B actually represented Type A W P W with a different amount of 'fusion than in the ECG labeled Type A Other objections to this case have been expressed [4] In our case the delta wave vector and main QRS vector in V_1 clearly chang ed from positive to negative therefore change in fusion cannot explain our patient's *ECG* *The* fact that the normal QRS seen in Fig 2 was not aber rant suggests that alternating bundle branch block was not responsible for the changing QRS morphology in Fig *3*

Review

Comparative mechanisms of action of antiarrhythmic drugs

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The clinical management of cardiac arrhythmias has undergone a great deal of change over the last ten years During this period coronary care units in many countries have shown that by early recognition and prompt treatment of arrhythmias the mortality rate in acute myocardial infarction can be reduced significantly The introduction of direct current countershock[1] revolutionized the acute management of most types of paroxysmal arrhythmias As a method however cardioversion is of limited value in the prophylaxis of recurrent arrhythmias and may be hazardous in the control of arrhythmias due to digitalis excess which is becoming an increasingly recognized cause of disturbances of cardiac rhythm and conduction[2] The emphasis is therefore once again shifting back to the use of anti arrhythmic drugs in the elective and prophylactic management of cardiac arrhythmias

It also appears that a greater reduction in the mortality rate in acute myocardial infarction than that achieved in coronary care units is unlikely to result from further refinements in the management of arrhythmias after infarct has occurred. Higher rates of survival in patients following infarction are likely to depend on advances in the treatment of cardiogenic shock and heart failure The area which now offers the greatest scope and challenge for an important reduction in the mortality rate in ischemic heart disease is sudden arrhythmic death occurring in ambulatory patients outside hospital Two thirds of all deaths in acute myocardial infarction occur before patients reach hospital or coronary care units[3] Evidence is accumulating to suggest that studies of the electrocardiogram (ECG)[4-7] may allow one to identify the group of patients particularly at risk from sudden death due to cardiac arrhythmia However even if such a group can be separated out confidently from the general population the reliability potency and safety features of existing antiarrhythmic drugs fall considerably short of the ideal properties for what may be a life long and costly commitment to drug therapy Recent advances nevertheless allow the hope that the ideal agent for widespread prophylactic use may eventually be found.[8]

It is not so very long ago that clinicians knew of only one type of antiarrhythmic drug quinidine and quinidine like compounds A plethora of antiarrhythmic agents now exists even though our knowledge of their fundamental mode of action in arrhythmias is still for the most part unknown A rational framework for interpreting the mode of action of the conventional as well as the newer antiarrhythmic agents is thus assuming increasing importance Classification of antiarrhythmic actions has always been a controversial subject In recent years it has become increasingly so with so many new compounds appearing on the pharmacologic horizon[9-11]

The classification to be presented in this review is based on an electrophysiologic approach considered previously[12,18,20] now extended and modified in the light of recent developments with a particular reference to the importance of the

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ventricular tachyarrhythmias with one to one conduction to the ventricles utilizing the Type A pathway resulting in extremely rapid heart rates In addition the possibility of ventricular tachycardia being induced by a conducted pre mature atrial beat arriving during the ventricu lar vulnerable period still remains

It is therefore quite fortunate for our patient that his arrhythmias have responded to medical therapy

Summary

A patient with W P W syndrome is presented who manifested both Type A and B configura tions The problems treating similar patients with resistant tachyarrhythmias are briefly dis cussed

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Vassalle[27] demonstrated that a decrease in potassium current was responsible for the spontaneous diastolic depolarization and Noble and Tsien[28] have correlated this process with a distinct potassium channel This type of analysis has been possible only with the recent application of the voltage clamp technique to cardiac muscle [23] Voltage clamp is already beginning to allow a better understanding of the precise mode of action of cardioactive drugs[29-31] in terms of ionic conductance changes In the future studies of antiarrhythmic drug actions using voltage clamp are likely to replace the relatively crude and simple electrophysiologic methods utilized in the past Advances have also been made at both level basic and clinical in our understanding of the origin of cardiac arrhythmias during the last ten years[3-35] There is now general agreement that arrhythmias occur either as a result of disordered impulse formation or disordered impulse conduction or a combination of both processes The actions of antiarrhythmic drugs may thus be interpreted in terms of their net effects on these two fundamental abnormalities in relation to the changes in ionic permeabilities that occur under the influence of the agents in known therapeutic concentrations

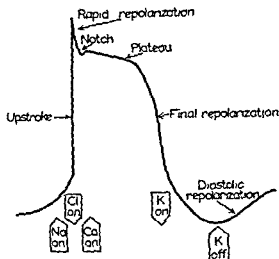


Fig 1 Diagrammatic representation of a cardiac action potential from Purkinje fibers illustrating the time sequence of major ionic events during one cardiac cycle The arrows below the diagram refer to the approximate time when the indicated ion is influencing membrane potential They point in the direction of the effect on the membrane potential upward for depolarization and downward for repolarization. (Reprinted with permission from Fozzard and Gibbons Am. J Cardiol 31 182 1973

Classes of antiarrhythmic agents

From such electrophysiologic considerations, the actions of commonly used antiarrhythmic drugs may be separated into three or possibly four[12,18-20,36] reasonably discrete categories Overlap in the subsidiary pharmacologic characteristics between groups is of course expected. Nevertheless from the point of view of clinical usage it appears helpful to construct a pharmacologic classification on the basis of major electrophysiologic determinants of antiarrhythmic actions[37] This approach is adopted in the present review and major antiarrhythmic actions are categorized in Table I

Group 1A Membrane depressant drugs Anti arrhythmic compounds in this class share the dominant electrophysiologic property of blocking the fast inward sodium current during the depolarization of the cardiac membrane This may be measured quantitatively either as a change in the maximal rate of rise of the action potential (Vmax or MRD) or a change in membrane responsiveness when the rate of rise is related to the level of the resting membrane potential from which the spike depolarization is initiated In practice both methods give virtually identical information concerning the mode of action of this class of antiarrhythmic drugs[38] A reduction in the rate of rise of the action potential or in membrane responsiveness is accompanied by a decrease in conduction velocity together with an increase in the threshold of excitability and in the effective refractory period of cardiac muscle In contrast the action potential duration is not usually affected but it may either shorten or lengthen although not to an extent which might alter the absolute refractory period. Drugs with membrane depressant actions are also local anesthetics though considerably higher concentrations are required to slow conduction in nerve than in cardiac muscle An additional feature which completes the over all antiarrhythmic profile of Group 1A drugs is the reduction in the slope of the pacemaker potential an effect which is usually seen in very much lower concentrations of the drugs than those which alter conduction velocity and excitability Because of their wide antiarrhythmic spectrum compounds in this general category are drugs of great clinical utility By depressing phase 4

Table I Classification of antiarrhythmic actions

Group	Membrane depressant (phases O + 4)*	Effect on action potential duration*	Sympatholytic effect*	Inhibitory effect on inward Ca ++ current*	Extracardiac actions
1A					
Quinidine	++++	Lengthen +	+	O	Anticholinergic
Procaine amide	++++	Lengthen +	O	O	Anticholinergic
Antazoline	++++	O	O	O	Antihistaminic
Carbamepazine	++++	Shorten +	O	O	Anticonvulsant
Disopyramide	++++	Lengthen +	O	O	Anticholinergic
Kö 1173	++++	O	O	O	Anticonvulsant
1B					
Diphenylhydantoin	++++	Shorten +	O	O	Anticholinergic and anticonvulsant
Lidocaine	++++	Shorten +	O	O	O
2 (β-adrenergic blockers)					
Propranolol	+	Shorten +	++++	O	Not relevant
Oxprenolol	+	Shorten +	++++	O	Not relevant
Alprenolol	+	Shorten +	++++	O	Not relevant
Practolol	Phase 4 only	O	++++	O	Not relevant
Pindolol	Phase 4 only	O	++++	O	Not relevant
3					
Bretylium	O	Lengthen ++++	Neuron blockade +	O	Not relevant
Amiodarone	O	Lengthen ++++	Non competitive +	O	Coronary dilator
4					
Verapamil	Phase 4 only	O	Non competitive +	++++	Coronary dilator

++++ Principal electrophysiological action + subsidiary electrophysiological action O no effect in presumed therapeutic concentrations

extracellular potassium ion concentration in modifying the actions of major antiarrhythmic compounds [13,19,21,22]

Background myocardial electrophysiology

The mechanism of action and therapeutic applications of antiarrhythmic drugs are best defined in terms of cardiac electrophysiology Significant advances continue to be made in our understanding of how the action potential is generated and propagated in the mammalian heart The current ideas have been well summarized recently by Fozzard and Gibbons [23]

The action potential in the heart results from sequential changes in ionic permeability across the membrane and to date eight different ionic channels have been identified Repolarization has a variable duration in different types of cardiac fibers (100 to 600 msec) and in terms of ionic currents it appears to be composed of several phases (Fig 1) The rapid depolarization phase of the action potential, lasting only a few milliseconds is the result of a sudden increase in the inward sodium current, the intensity of which, as measured by the maximal rate of depolarization (MRD) or maximum dV/dt of the upstroke (Vmax), is a function of the membrane potential from which the spike takes off This relationship subsequently termed (membrane responsiveness) was clearly demonstrated by Weidmann [24] (Fig 2) who showed that until the membrane repolarized to about −50 mV or a more negative voltage level it could not be reactivated no matter how large the excitatory stimulus This level of repolarization thus defines the end of the absolute refractory period in cardiac muscle Interventions which shorten the action potential duration (anoxia halothane acetyl choline) are proarrhythmic by decreasing the absolute refractory period and conversely, interventions which prolong the duration of the action potential (e g bretylium, amiodarone) are antiarrhythmic by lengthening the absolute refractory period

The existence of an identifiable depolarizing ionic channel for inward calcium current in the heart has recently been confirmed [5,26] and a clearer understanding of the mechanism of the pacemaker potentials is now also emerging

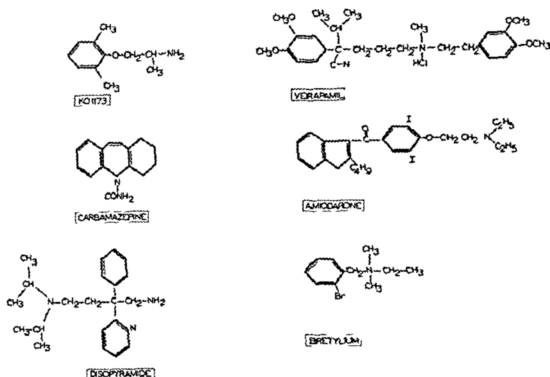


Fig 3 Chemical structures of newer antiarrhythmic compounds discussed in the text.

ties A variety of clinical arrhythmias have been found to respond to antazoline[47-49] It appears to be antiarrhythmic by depressing the maximal rate of depolarization of the cardiac action potential although its detailed electrophysiologic effects on heart muscle have not been extensively evaluated Similarly its precise therapeutic usefulness and potency in relation to those of better known antiarrhythmic drugs have not been clearly established. It would therefore seem that its pharmacologic and clinical properties merit further investigation

Disopyramide (Fig 3) is another compound whose antiarrhythmic properties have been known for some years[50] but are only beginning to be utilized in the clinic[51,52] The drug s antiarrhythmic action and electrophysiologic effects appear to be very similar to those of quinidine As in the case of quinidine disopyramide has weak anticholinergic actions and may therefore increase the heart rate in some patients. It causes less hypotension and has been claimed to be safer than quinidine However before disopyramide is accepted for wider clinical use its potential value in therapeutics needs to be evaluated against the background of experience with the conventional and the newer antiarrhythmic compounds

Carbamazepine (Fig 3) was initially introduced with clinical therapeutics as an anticonvulsant but soon was found to be extremely effective in the management of trigeminal neuralgia Its antiarrhythmic potential was investigated by Steiner and colleagues[53] who reported detailed electrophysiologic studies with the compound in isolated canine myocardial and Purkinje fiber preparation Therapeutic concentrations of the drug in the clinical context still remain to be defined but in the range of the concentrations which were effective in correcting a variety of experimental arrhythmias carbamazepine was found to reduce Purkinje fiber automaticity and membrane responsiveness with a moderate degree of shortening of the action potential duration The drug has been found to be at least as effective as diphenylhydantoin in reverting arrhythmias due to ouabain toxicity or those occurring after coronary artery occlusion[54] Clinical experience with carbamazepine is however limited although it has been claimed to be the only antiarrhythmic compound which is of prophylactic value in the hereditary syndrome of prolonged Q Tc interval of the ECG with the

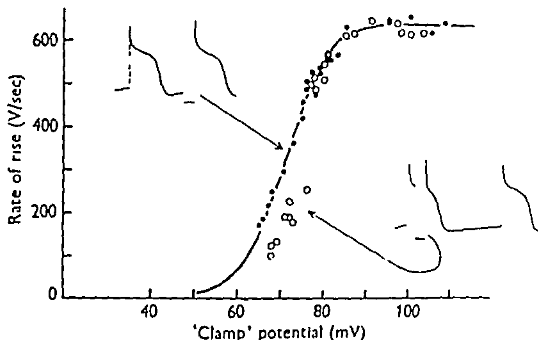


Fig 2 Relationship between clamp potential and maximal rate of rise of action potential Solid circles values obtained with clamp in diastole Clear circles values obtained with clamp during systole (Reprinted with permission from Weidmann J Physiol 127 213 1955)

depolarization they can control arrhythmias due to enhanced automaticity and by altering the refractory period they are likely to be effective in aborting re entrant arrhythmias The salient features of the individual drugs in this category may now be outlined briefly

Quinidine is the prototype of antiarrhythmic drugs with membrane depressant actions In the days before transmembrane potentials could be recorded from single cardiac fibers it was a generally held belief that its antiarrhythmic action was due to its effect in prolonging the action potential duration It is now clearly established[39-41] that concentrations of quinidine corresponding to the therapeutic' plasma levels (2 to 6 μg per milliliter cause only a trivial alteration in repolarization in relation to the very marked delay they produce in conduction velocity and the effective refractory period of heart muscle

Recent correlations of serum levels in patients treated with the drug with changes in the time expanded oscilloscopic display of the QRS and Q Tc intervals of the ECG have confirmed the over all results of in vitro studies Concentrations of quinidine in the therapeutic range prolonged the QRS duration and delayed conduction velocity as the dominant effects while the changes in the Q Tc interval were relatively minor[42] Such studies thus allow the conclusion that a gross change in the Q Tc interval of the ECG during quinidine therapy is a sign of toxicity rather than a consistent accompaniment of the drug s salutary antiarrhythmic action in the clinic

Procainamide shares all the electrophysiologic properties of quinidine in concentrations (4 to 7 μg per milliliter which are of therapeutic relevance[43] In vivo and in vitro correlations of its pharmacologic effects with respect to the electrophysiologic and electrocardiographic parameters have recently been reported by Rosen Gelband and Hoffman,[44] using their newly developed elegant technique of blood perfusion of isolated canine Purkinje fibers[45]

Over the last ten years procainamide has emerged as an important antiarrhythmic drug in the treatment of ventricular arrhythmias especially in the setting of the coronary care unit[8]

Frequent administrations of the drug are however necessary to achieve sustained effective plasma concentrations and the upper range of the therapeutic levels are extremely close to those causing toxic effects Monitoring of plasma concentrations of procainamide is thus often necessary and this limits the scope for its widespread use in major prophylactic programmes Moreover the incidence of the systemic lupus syndrome during prolonged treatment is high[4]

Antazoline is an antiarrhythmic compound with antihistaminic and local anesthetic proper

the contrary in concentrations up to 5 μg per milliliter it actually *increased* membrane responsiveness and conduction velocity and caused an abbreviation of both the action potential duration and the effective refractory period. These changes were particularly prominent in depressed cardiac fibers. In direct conflict with these over all results are the observations of Sano and associates[62] who found that DPH in concentrations between 1 and 10 μg per milliliter had actions on the cardiac muscle not dissimilar to those of quinidine producing a marked retardation in conduction velocity and the maximal rate of depolarization (MRD) of the action potential in ventricular muscle

Similarly Bigger and his colleagues[60,63] and Davis and Temte[64] subsequently reported that therapeutic concentrations of lidocaine (1 5 to 6 μg per milliliter did not depress membrane responsiveness in atrial, ventricular or Purkinje fibers As in the case of DPH lidocaine often enhanced membrane responsiveness and conduction velocity It shortened the effective refractory period (ERP) but not to the same extent that it accelerated repolarization This disproportionately greater shortening of the action potential duration thus implied a net prolongation of the ERP Interpreted in this way these changes in the cardiac action potential together with the increase in membrane responsiveness due to either DPH or lidocaine have come to be regarded as an important antiarrhythmic mechanism[56]

The validity of the experimental results on which these interpretations are based has now been questioned on the grounds that perfusion media utilized in the various studies with DPH and lidocaine had low (2 7 to 3 0 mM) potassium concentration[13,19,21,22,65] Changes in extracellular potassium levels near the extremes of physiologic limits may have profound effects on the excitability and other properties of the myocardial cell[66,67] Watanabe Dreifus and Likoff[68] and Watanabe and Dreifus[69] found that low concentrations of potassium in the perfusion medium greatly minimized or even reversed the electrophysiologic effects of quinidine and other similarly acting antiarrhythmic drugs The effect was found to be particularly striking on spike depolarization

It was therefore not altogether surprising when a similar dependence of the electrophysiologic actions of DPH on extracellular levels of potassium was reported independently by Jensen and Katzung[70] and Singh and Vaughan Williams[19] In parallel studies the actions of lidocaine were also found to exhibit virtually identical dependence on the potassium levels of the perfusion medium[13,19,21,22] When media containing potassium within the generally accepted levels were used the cardiac effects of the therapeutic concentrations of DPH and lidocaine were found to be very similar to those of quinidine[19,70,71] The salient findings are summarized in Fig 4 and a typical example of the potassium dependence of the action of DPH is illustrated in Fig 5 The effects of only two concentrations of potassium are presented here although the changes observed were found to be linearly related to the potassium concentrations used[72]

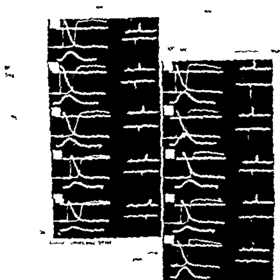


Fig 5 Effect of DPH on atrial intracellular potentials in 5 6 and 3 mM KCl In each frame the traces depict the following Left horizontal trace zero potential middle traces, intracellular potentials at slow and fast sweep speeds bottom trace isometric contractions Right upper trace stimulus artifact from electrode on left atrium and action potential recorded from surface of right atrium lower trace differential of intracellular record (max dV/dt the depth of the signal being proportional to the maximum rate of depolarization) In 5 6 mM KCl DPH 5 to 20 mg per liter greatly reduced the dV/dt whereas this effect was virtually completely abolished in 3 mM KCl (From Singh.[13])

The over all findings with different levels of external potassium thus serve to resolve some of the reported discrepancies in the electrophysiologic actions of DPH and lidocaine on

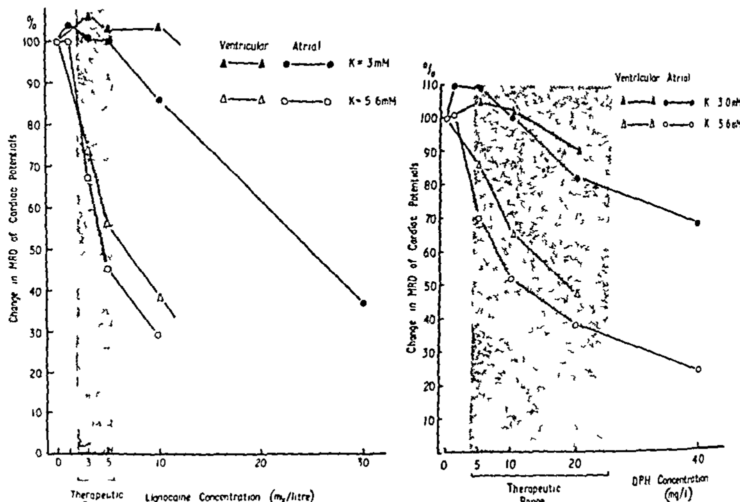


Fig 4 Dose response curves for lidocaine (left) and DPH (right) on the maximum rate of depolarization of atrial and ventricular muscle in 3 and 5 6 mM solutions In accepted "therapeutic" concentrations both drugs reduce the MRD of the action potential in isolated heart muscle preparations (Reprinted with permission from Singh and Vaughan Williams. Circ Res 29 286 1971)

tendency to recurrent ventricular tachycardia and fibrillation [55] Evidence discussed elsewhere[14] also suggests that carbamazepine may be an effective agent for the management of certain types of supraventricular tachycardias Clearly the antiarrhythmic potency of the drug requires clinical and experimental evaluation

Ko 1173 is an anticonvulsant drug which has a striking structural similarity to lidocaine (Fig 3) with which it shares major electrophysiologic actions on cardiac muscle and nerve [56] It is therefore not surprising that its antiarrhythmic spectrum closely resembles that of lidocaine [56 57] its main advantage over lidocaine being the fact that it might be possible to use the drug by the oral route in which event it may prove of value in long term prophylactic antiarrhythmic regimes

Group 1B Lidocaine and diphenylhydantoin The antiarrhythmic actions of diphenylhydantoin (DPH) and lidocaine have recently given rise to considerable controversy which is still not adequately resolved [13 21 2 38 58] For the present it would therefore be convenient to classify their actions in a discrete category although a close similarity of their pharmacologic properties to those of quinidine at least with respect to their fundamental effects on the cardiac membrane is difficult to ignore [19]

Most investigators however agree that, like quinidine lidocaine and DPH do depress spontaneously depolarizing Purkinje fibers even in very low concentrations [59 60] and this may form the basis for their efficacy in aborting arrhythmias due to enhanced automaticity The major discrepancies in the literature have been in the precise effects of DPH and lidocaine on the gross electrophysiologic parameters such as membrane responsiveness and conduction velocity in isolated preparations For example Bigger and his colleagues[59 61] found that in concentrations up to 13 8 μg per milliliter (therapeutic 5 to 25 μg per milliliter) DPH neither decreased membrane responsiveness and conduction velocity nor elevated the electrical threshold of excitability On

Table II Correlation of membrane depressant effects of β blocking drugs with their therapeutic plasma levels in man

β receptor blocking drug	*Approximate plasma half life (hr)*	*Therapeutic plasma levels in patients*	*Oral daily dose (mg)*	*Threshold in vitro concentration producing membrane depressant effects† (µg/mL)*
1 Propranolol	3	25 250 ng/ml	40 80 q i d	0 15
2 Alprenolol	3	10 15 ng/ml	100 q i d	0 15
3 Oxprenolol	3	80 100 ng/ml	40 60 q i d	0 3
4 Pindolol	3	5 25 ng/ml	5 q i d	1 5
5 Practolol	10	1 5 5 µg/ml	200 400 b d	30 100

These levels are likely to provid complete pr tect on for the effects of endogenous sympathetic stimulation
†Based on depressant ctions of β b ockers in electrically driven isolated heart muscle p epa at ons.

resting heart rate decreases with β blockade and ectopic tachycardias are either slowed or con verted to sinus rhythm.

Very much higher concentrations of β blockers produce local anesthesia on nerve and the characteristic membrane depressant effects on heart muscle These effects are present to varying degrees in most agents and are of course independent of their receptor blocking potencies

Shortly after their introduction the antiar rhythmic actions of β receptor antagonists were attributed exclusively to their sympatholytic effects Later it was found that the levo and the dextro isomers of β blockers were equipotent an tiarrhythmic drugs in the experimental animal even though the dextro isomer was largely devoid of β receptor blocking property [79,80] This led to the belief that β blockade was irrelevant in the antiarrhythmic actions of β receptor antagonists and that their membrane depressant actions quinidine like) were solely responsible for their beneficial effects in arrhythmias Recent clinical experiences with several isomers have not supported this claim The dextro isomers of propranolol and alprenolol were found to be weak antiarrhythmic compounds in clinically realistic doses[81,82] and when they did have signifi cant actions in very much higher doses, side effects were frequent and potentially dangerous These studies with the dextro isomers of β blockers are of considerable interest in so far as they go a long way toward establishing the orig inal concept that β blockade is an important determinant of the antiarrhythmic actions of β receptor antagonists and that their membrane actions may be of relatively minor significance in the usual clinical context This is further sup ported by the studies which have attempted to correlate plasma levels of β blockers with their quantitative pharmacologic effects (Table II)

In the usual pharmacologic doses the levels of propranolol achieved in plasma (25 to 250 ng per milliliter) fall short of the order of concentrations which have membrane depressant actions by a factor of at least 100 This difference will be further accentuated by plasma protein binding in the case of propranolol alprenolol and ox prenolol Two conclusions may be drawn from these observations (1) The depression of the sinus pacemaker appears to be the only elec trophysiologic effect which might be expected to occur with therapeutic concentrations of β blockers (ectopic pacemakers may of course be sensitive to even lower concentrations) (2) The membrane depressant actions are not likely to be manifest with the order of plasma levels achieved with the commonly used dose schedules of β blockers On the other hand the possibility that such intrinsic or direct depressant actions of β blockers may become apparent in very much lower concentrations in patients with severe myocardial damage cannot be excluded. The relative roles of adrenergic receptor antagonism and membrane depressant effects in reversing arrhythmias under different conditions therefore require further study

Group 3 Amiodarone and bretylium It is generally accepted that the length of the ab solute refractory period is determined largely by

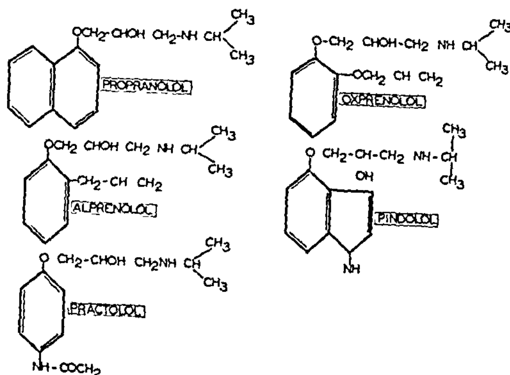


Fig 6 Chemical structures of some β adrenergic receptor antagonists discussed

heart muscle They also bring into sharp focus the importance of the levels of extracellular potassium ion concentration in determining the mode of action of the major class of antiarrhythmic drugs They do not, however account for the improvement in conduction velocity and membrane responsiveness seen with low concentrations of DPH and lidocaine even when the potassium levels are appropriate

It seems unlikely that the improvement in A V conduction seen occasionally with lidocaine in the clinic[73] and commonly with DPH has a direct relationship to the membrane actions of the two drugs The clinical setting in which this effect is manifest needs to be carefully appraised and the possibility exists at least in the case of lidocaine that improvement in A V conduction by the drug may be due to concomitant hypokalemia A V block following lidocaine therapy is occasionally encountered[72] and the drug is contraindicated in heart block In the case of DPH the associated autonomic actions may be of greater importance in determining the net pharmacologic effects of the drug For example Bigger, Strauss and Hoffman[74] found that the shortening of the A V conduction by DPH was attenuated by pretreatment with atropine and propranolol and did not occur in the reserpinized animals Other studies[75,76] also indicated that removal of the automatic influence on the heart converted the facilitatory action of DPH on the AV node to a depressant one A further difficulty in interpreting the action of DPH in whole animals is the important extent to which the drug is sequestered by serum proteins The clinical significance of this is largely unknown although studies utilizing the technique[45] of blood perfusion of isolated preparations of heart muscle will be critical in defining the precise electrophysiologic effects of DPH and lidocaine or other antiarrhythmic compounds whose actions may exhibit major variations under in vitro and in vivo experimental conditions

Group 2 β adrenergic receptor antagonists. This group of drugs (Fig 6) now have an established place in the treatment of a variety of cardiac arrhythmias[77] The mechanisms of their antiarrhythmic actions have been reviewed in some detail elsewhere[14,15,78] β receptor blocking drugs do not constitute a homogeneous group and a minor alteration in the chemical structure of different compounds has produced important changes in their pharmacologic properties Their over all actions depend greatly on their plasma levels In very low concentrations their only demonstrable action is the competitive antagonism of β receptors The sole electrophysiologic effect in these 'blocking concentrations is the reduction in the slope of the pacemaker potential, sinus or ectopic so that the

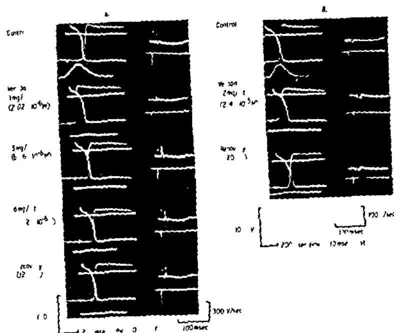


Fig 8 Effect of intravenous verapamil in a patient with supraventricular tachycardia (150 per minute) Reversion to sinus rhythm occurred within two minutes after 10 mg of verapamil was given. (From Singh B N and Heng M K 1973 Unpublished observations)

trophysiologic effects on rabbit atrial muscle They concluded that its antiarrhythmic action was due to its adrenergic neurone blocking property This is not in line with the findings of Cervoni Ellis and Maxwell[94] who showed that bretylium s capacity to elevate fibrillatory threshold in dogs was not abolished by chronic denervation or reserpine Furthermore Romhilt and his colleagues[95] have reported a clear cut dissociation between the hypotensive (hence neurone blocking) and antiarrhythmic actions of bretylium.

Any explanation advanced to account for bretylium s antiarrhythmic action must also allow for the fact that the drug is effective in ventricular and *not* in supraventricular arrhythmias[72] It is thus of particular importance to know the electrophysiologic actions of bretylium on ventricular muscle and Purkinje fibers. These have been clearly delineated by Wit Steiner and Damato[96] as well as Bigger and Jaffe[97] Both groups showed that bretylium did not depress automaticity in Purkinje fibers the only significant effect being the very striking prolongation that it produced in the repolarization phase of the action potential In "depressed fibers bretylium hyperpolarized the membrane and improved membrane responsiveness effects which may be related to the release of catecholamines induced by the drug

The effect on the ventricular repolarization may thus be of twofold significance (1) the fact that the phenomenon is not observed in atrial muscle may explain why bretylium does not antagonize supraventricular tachyarrhythmias and (2) the prolongation of the action potential duration with the associated increase in the effective refractory period in all probability constitutes at least in part the mechanism of the drug s antiarrhythmic action

Group 4 Selective calcium antagonists The introduction of verapamil (Isoptin Cordilox Knoll AG Germany Fig 3) a phenethylamine coronary vasodilator for the treatment of arrhythmias appears to be a new departure in the characterization of antiarrhythmic actions[13,20] Therapeutically this compound was initially used as an antianginal drug[98] but recently has been gaining prominence as the most effective agent (Fig 8) in the acute treatment of supraventricular tachycardias[99,100]

In the experimental animal verapamil was found to be an effective agent in protecting both against ouabain induced and chloroform epinephrine arrhythmias[20,101,102] Of particular interest is the report by Kaumann and Aramendia[103] that ventricular fibrillation never occurred after coronary ligation in dogs pretreated with

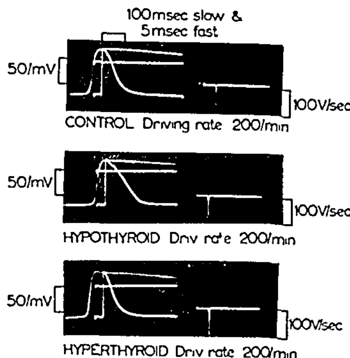


Fig 7 Effects of altered thyroid state on intracellular atrial potentials in the rabbit Descriptions of intracellular records as for those in Fig 5 but surface electrograms and isometric contractions have not been recorded All records were taken at the same driving frequency of stimulus to eliminate the differences in repolarization due to changes in rate of con traction Marked delay in repolarization was seen in hy pothyroidism and the converse in hyperthyroidism (Reprinted with permission from unpublished work of Dr J Gy Papp and Dr E M Vaughan Williams 1969)

the time course of repolarization in cardiac mus cle Accelerated repolarization shortens the ab solute refractory period and if sufficiently marked as with acetyl choline in atrial muscle[41] or with halothane in Purkinje fibers [83] may result in the development of cardiac arrhythmias Delay in repolarization might therefore be ex pected to be anti arrhythmic *This is somewhat* contrary to what is generally believed since Q Tc prolongation in situations like the Jervell Lange Nielsen syndrome are known to pre dispose to recurrent ventricular arrhythmias [84] Drugs such as Melleril[85] or toxic concentrations of quinidine, which also prolong the Q Tc inter val of the ECG, occasionally but not regularly produce ventricular fibrillation Nevertheless several lines of evidence suggest that isolated Q Tc prolongation *per se* is not necessarily proar rhythmic and that the reverse situation of a reduced incidence of arrhythmias in the context of "pure' Q Tc prolongation might be a more common occurrence

Hypocalcemia is an important cause of gross prolongation of the Q Tc interval of the ECG but does not appear to be associated with an in creased incidence of ventricular arrhythmias. The β blocking drug, sotalol, produces consider able delay in repolarization of the cardiac action potential in large doses[12] but even with repetitive ventricular stimulation it is extremely difficult to induce cardiac arrhythmias in anesthetized dogs pretreated with the compound [72]

It is well known that in thyrotoxicosis atrial ar rhythmias are common and they are rare in hy pothyroidism Freedberg Papp, and Vaughan Williams[86] recently found that in experimentally *induced thyrotoxicosis in rabbits the atrial in* tracellular potentials were markedly abbreviated in duration and in hypothyroidism they were sig nificantly prolonged (Fig 7) No other elec *trophysiologic parameters in the atrial muscle* were affected by variations in the thyroid state A situation analogous to the effects of hypothyroid ism on cardiac intracellular potentials was later found with the chronic administration of the an tianginal drug, amiodarone (Fig 3), which pro duced "pure' prolongation of repolarization in atrial as well as ventricular fibers [11] Amiodarone has since been found to be a potent antiar rhythmic drug in the clinic[87] but despite the fact that it does prolong the Q Tc interval of the ECG in patients,[88] ventricular arrhythmias have not been encountered during long periods of treat ment in large numbers of patients [89] Amiodarone is not a local anesthetic on nerve or cardiac membrane[11] and it does not have competitive β receptor blocking properties [90] We have therefore attributed its antiarrhythmic actions to its prop erty of prolonging the action potential duration *with the consequent lengthening of the effective* refractory period [11]

The antiarrhythmic compound which has re cently created a great deal of clinical and experi mental interest is *bretylium tosylate* [9 91 92] The precise mode of its antiarrhythmic action is still not entirely certain although from the purely electrophysiologic aspects it may, at least tenta tively, be classed among drugs which produce iso lated prolongation of the refractory period by lengthening the *action potential* duration It must however be emphasized that bretylium ex hibits striking differences between its effects on atrial muscle and those on ventricle muscle or Purkinje fibers For example Papp and Vaughan Williams[93] found that bretylium in clin ically realistic concentrations had no elec

Summary

The antiarrhythmic actions of different compounds are best compared in terms of their dominant electrophysiologic effects on myocardial fibers from different parts of the heart Such primary actions may be modified considerably by changes in the serum electrolyte concentrations pH interactions with serum proteins, or other extracardiac factors Clinically however it appears useful to categorize antiarrhythmic drugs into four groups in terms of their currently known mechanisms of action. Quinidine is the prototype of Group 1 drugs Its main effect is the reduction of the maximal rate of depolarization of the cardiac action potential so that it slows conduction velocity and increases the effective refractory period with only minor effects on repolarization Procainamide disopyramide carbamazepine and Kö 1173 all have similar effects to those of quinidine on heart muscle Lidocaine and diphenylhydantoin may be considered to constitute a subgroup (Group 1B) of quinidine like" drugs In small concentrations they increase membrane responsiveness but in concentrations in the therapeutic range they have a quinidine like depressant action on the cardiac membrane particularly if serum levels of potassium are physiologically appropriate Group 2 drugs are exemplified by β adrenergic receptor blocking compounds In blocking concentrations their only electrophysiologic effect is the reduction in the slope of the pacemaker potential in very much higher concentrations they reduce the maximal rate of depolarization of the cardiac action potential but the precise clinical significance of this is still uncertain Amiodarone and bretylium prolong the duration of the action potential in the ventricular muscle and Purkinje fibers without causing a significant change in other electrophysiologic parameters This leads to a 'pure prolongation of the absolute refractory period which may be regarded as an independent antiarrhythmic mechanism (Group 3) Verapamil a novel antiarrhythmic compound, is a specific calcium antagonist in the heart It does not reduce the maximal rate of depolarization of the action potential but slows the spontaneous diastolic depolarization in heart muscle The effects of verapamil are sufficiently different from those of other known agents to allow the tentative conclusion that its fundamental mode of action represents a fourth (Group IV) class of antiarrhythmic action

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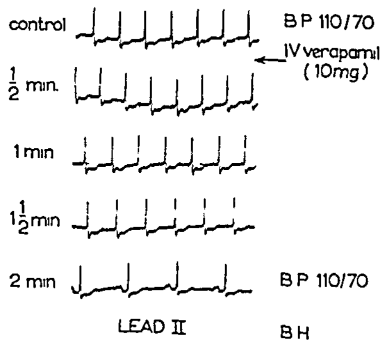


Fig 9 Effects of verapamil on ventricular intracellular potentials Description as for Fig 6 In clinically realistic concentrations the only effect of the drug is to reduce myocardial contractions with no effect on MRD or conduction velocity

verapamil and the animals subsequently survived for many months Apart from the initial antiarrhythmic effects of verapamil, it is possible that the drug enhances long term survival following coronary occlusion in dogs by an additional mechanism such as reduction in the size of infarction which has been shown to occur with verapamil [104]

The antiarrhythmic action of verapamil is not accounted for by any of the known mechanisms already described Verapamil is not a competitive β adrenergic receptor antagonist nor is it akin to bretylium or amiodarone Its only resemblence to other antiarrhythmic agents is the depression of the slope of the pacemaker potential that it produces[13] in common with quinidine and other similar drugs It was found[13,20] that although verapamil has local anesthetic activity 1 6 times greater than that of procaine it has no effect on the maximal rate of depolarization of the action potential or membrane responsiveness in atrial and ventricular muscle (Fig 9) except in concentrations considerably in excess of those likely to be encountered in clinical practice [105] In clinically realistic concentrations verapamil did not influence intra atrial or intraventricular conduction, action potential duration or electrical threshold [20] It was nevertheless of interest to find that in low concentrations it had a selectively depressant effect on the sinus node studies in vitro[13] or on the atrioventricular node studied with His bundle electrocardiography [72] Little is known about the results of electrophysiologic studies on cardiac nodal fibers although voltage clamp data already available have clearly shown that verapamil blocks the inward calcium but not the fast sodium current in ventricular and Purkinje fibers [30] Fleckenstein[106] has further demonstrated that this selective reduction in calcium conductance is a membrane phenomenon as it does not occur in 'skinned myocardial fiber preparations

The selective block of calcium entry into the myocardial cell accounts for the action of verapamil on excitation contraction coupling as well as its depressant effect on myocardial contractility [13,20] The negative inotropic action does not however, preclude its clinical use in arrhythmias Even with intravenous administration very little cardiovascular depression is encountered in patients with heart disease [99,100] It is possible that a rapid sequestration of the drug by plasma proteins diminishes its potential negative inotropic propensity by minimizing the concentrations actually remaining in association with the myocardial tissues

The question which remains to be resolved is whether the inhibition of the inward calcium current in the heart by verapamil is relevant to the antiarrhythmic action of the drug Vaughan Williams[36] has discussed the possible implication of the abnormalities of calcium fluxes in the genesis of arrhythmias Although it is largely speculative it has been suggested elsewhere[70] that the possibility exists that an abnormal influx of calcium could produce a partial depolarization which might contribute to the development of an aberrant spike The attraction of this hypothesis is that such a depolarization could occur even when the normal sodium carried depolarization process is largely inactivated during the plateau. Unfortunately, there is no substantial evidence to support it. However, if such calcium currents can be responsible for out of phase extrasystoles interference by a drug such as verapamil with inward calcium movement across the membrane would not only account for its negative inotropic action but would also constitute a fourth class of antidysrhythmic action

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Electrocardiographic changes during hyperventilation resembling myocardial ischemia in patients with normal coronary arteriograms

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Exercise stress testing has become a useful aid to the clinician in the diagnosis of ischemic heart disease Electrocardiographic criteria defining a positive test for myocardial ischemia are now well established[1-3] The varied effects of hyperventilation on the RST waves of the electrocardiogram have also been reported[4-6] it is generally believed that electrocardiographic changes occurring during hyperventilation are not easily mistaken for changes of ischemic origin

We have encountered seven instances in which coronary artery disease was believed to be present on the basis of equivocal histories and exercise tests that were interpreted as diagnostic or suggestive of ischemia in each case normal coronary vessels were found during elective coronary arteriography Review of these patients records revealed that hyperventilation produced alterations in the electrocardiogram which mimicked the changes produced by myocardial ischemia In each patient similar if not identical changes were observed during exercise leading to false positive interpretation of the stress test These cases and the diagnostic difficulties they present form the basis of this report.

Methods

Patients referred to this institution for evaluation of coronary artery disease receive a complete history physical examination roentgenograms of the chest, and a 12 lead electrocardiogram (ECG) Unless accelerating (pre infarction) angina pectoris is present all patients undergo treadmill (TM) exercise testing Those taking digitalis preparations are instructed to discontinue them three weeks prior to hospitalization The patient s clinical symptomatology together with the results of the stress test constitute the basis from which the decision to perform coronary and left ventricular angiography is made Coronary arteriography is performed only in those patients whose angina is unstable or poorly controlled on medical management Studies are not carried out in asymptomatic patients regardless of history of past myocardial infarction even though they may have a positive TM test Angiographic studies *are* performed in patients whose chest pain is atypical in location character and response to antianginal medication but whose TM tests are positive

Prior to TM testing a control ECG is obtained in the sitting position using a precordial lead system corresponding to V_5 The patient is then instructed to hyperventilate for as long as is tolerable Continuous tracings are recorded during hyperventilation and at 30 second intervals during recovery The hyperventilation period, usually ranging from 40 to 90 seconds is terminated when lightheadedness and/or fatigue occur If nonspecific RST changes occur during hyperventilation which might hinder proper interpretation of RST alterations during exercise the changes are minimized or abolished by moving the exploring precordial lead medially or laterally A second hyperventilation test is then performed after which an electrocardiographically monitored, multistage motor

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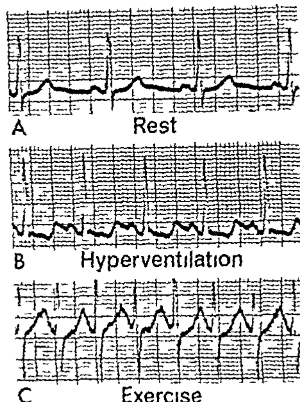


Fig 3 A through C A Resting electrocardiogram prior to stress testing is normal B During hyperventilation at heart rate 110 per minute marked ST segment depression occurs thus making interpretation of ST changes during stress invalid, using this precordial lead. C After repositioning of the exploring electrode exercise test during Stage V shows no abnormalities

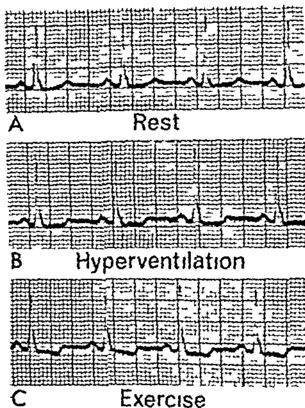


Fig 4 A through C A Baseline tracing prior to hyperventilation B Hyperventilation produces ST segment flattening C At a similar heart rate of 80 per minute during exercise ST segment depression is more marked.

Case reports

Case 1 A 40 year-old man gave a 10 year history of chest pain related to emotional stress and exertion A submaximal stress test performed on a bicycle ergometer by his private physician was interpreted as positive and the patient was referred for coronary arteriography Physical examination laboratory data, and ECG were within normal limits (Fig 1A) A 70 second period of hyperventilation prior to TM testing produced segmental ST depression (Fig 1B) similar to that seen in the previous bicycle test During TM exercise the patient reached Stage V and attained a heart rate of 185 per minute Segmental ST depression occurred similar to that seen during hyperventilation (Fig 1C) no chest pain occurred. Coronary angiograms were normal

Case 2 A 58 year old male house painter was referred with a three year history of precordial pressure radiating into the left arm The pain although related to exertion, lasted hours or days and did not respond to sublingual nitrates Increasing severity of the pain had totally incapacitated the patient during the three months prior to admission A Master's two step test performed elsewhere was interpreted as positive Physical examination, laboratory data and a resting ECG were normal (Fig 2A) A TM test was terminated in Stage IV (heart rate 165 per minute) because of fatigue Segmental ST depression observed at two minutes into the recovery period was interpreted as diagnostic of ischemia. Coronary arteriography demonstrated normal vessels A second TM test was performed, preceded this time however by a prolonged, 260 second period of hyperventilation. ST segmental depression developed during hyperventilation (Fig 2B) the changes were less remarkable however than those seen in the recovery period following subsequent exercise (Fig 2C)

Case 3 A 33 year old hypertensive male with hypercholesterolemia and a heavy smoking history had had two months of exertional dull pressing chest pain radiating to the left arm and lower jaw and relieved by rest Physical examination was normal A TM test during which the patient reached Stage IV (heart rate 175 per minute) was normal as were subsequent coronary arteriograms The patient was advised that he did not have coronary artery disease and that he should resume normal activity discontinue smoking and follow a low cholesterol diet

The patient was re evaluated two years later Although he had been free of chest discomfort a positive Master's two step test performed by his private physician had resulted in inability to obtain insurance Physical examination was again normal Prior to TM testing hyperventilation for 60

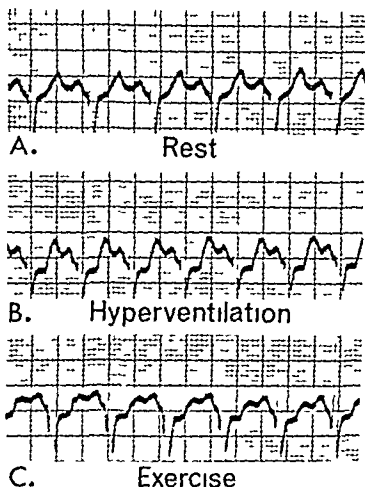


Fig 1 A through C A Resting tracing obtained prior to treadmill testing Heart rate is 125 per minute B Segmental ST depression occurs during hyperventilation at heart rate of 150 per minute C During treadmill exercise at heart rate 140 per minute similar ST segment depression occurs.

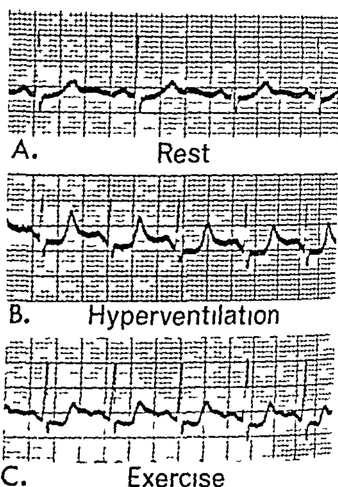


Fig 2 A through C A Baseline tracing showing no abnormalities B Hyperventilation test showing ST segment flattening at heart rate of 110 per minute C Significant ST depression observed at three minutes into the recovery period after stress testing The heart rate is 110 per minute The exercise test was considered diagnostic of ischemia by a physician having no knowledge of the patient s coronary arteriograms.

driven TM test is carried out. Treadmill speed and grade are increased every three minutes to provide progressive increments of exercise load[1] The stress is continued until the appearance of ischemic ST changes (flattening or downward *sloping of the ST segment greater* than 1 mm) attainment of a heart rate considered to be maximal for a given age, the appearance of ventricular tachyarrhythmias or severe chest pain shortness of breath, or hypotension precluding further exercise regardless of electrocardiographic findings

Results

Patients selected for inclusion into this study had to satisfy three criteria (1) hyperventilation test performed just prior to (2) treadmill exercise test and (3) selective coronary and left ventricular angiography during the same hospital admission In over 1,000 records reviewed 238 met these criteria Of the 238, 192 had abnormal coronary arteriograms and 185 of these (97 per cent) had no ECG changes during hyperventilation, seven (3 per cent) had ECG changes of ischemia during hyperventilation In contrast of 46 patients with normal coronary arteriograms 15 per cent (7/46) had ischemic appearing electrocardiograms during hyperventilation their subsequent exercise tests were interpreted as positive for or suggestive of ischemia or inconclusive TM tests were normal and there were no hyperventilation changes in the remaining 39 patients with normal coronary arteriograms The statistically significant difference between those patients have ischemic ST T changes during hyperventilation and normal coronary arteries, and those with similar hyperventilation changes and diseased coronary vessels was remarkably high (two sample proportion test $Z = 2\ 75$ P less than 005)

The patient underwent TM testing prior to which she hyperventilated in the sitting position for 50 seconds reaching a heart rate of 80 per minute ECG changes during hyperventilation consisted of slight J point depression and ST segment flattening (Fig 4B) The ECG changes occurring during TM testing were pronounced (Fig 4C) in view of the hyperventilation test, however the interpretation of the treadmill test was nondiagnostic Because of a history suggesting atypical pain, possibly cardiac in origin, and failure of exercise testing to document unequivocal ischemic changes, coronary arteriography was performed and was normal

Case 5 A 44 year old nurse had a one year history of nonexertional crushing midsternal chest pain which radiated to the jaw and arms Pain occurred at night lasted 20 to 30 minutes and was relieved only by narcotic analgesics. A bicycle exercise test performed elsewhere was normal Physical examination and laboratory data were normal The ECG demonstrated minor nonspecific ST changes (Fig 5A) Prior to TM testing a 30 second period of hyperventilation produced downsloping ST segments (Fig 5B) similar changes were seen during the treadmill test (Fig 5C) Coronary arteriograms demonstrated normal vessels

Case 6 A 42 year old woman gave a two-month history of nonexertional frequent severe substernal distress which waxed and waned and was never entirely absent She was able to perform her household and job duties satisfactorily Physical examination, laboratory data and an ECG were within normal limits (Fig 6A)

A TM test was performed to document the clinical impression of noncardiac pain. Prior to stress testing the patient hyperventilated for 60 seconds during which no ST T changes were observed (Fig 6B) After 90 seconds of graded exercise testing the patient complained of chest discomfort and fell to the floor The episode was unaccompanied by hypotension diaphoresis arrhythmia or unconsciousness TM test was interpreted as diagnostic of ischemia (Fig 6C) and coronary arteriography was performed. During the early part of the cardiac catheterization procedure the patient complained constantly of pain, skipped beats and extreme fearfulness Before any contrast medium was given, she began to hyperventilate spontaneously reaching a heart rate of 145 per minute Electrocardiographic monitoring during this period disclosed typical ST T changes of ischemia (Fig 6D) chest pain did not occur Selective coronary and left ventriculography were normal It was concluded that the patient indeed had chest pain of noncardiac origin, and that the positive TM test resulted from hyperventilation alone Presumably inadequate heart rate during her initial pre exercise hyperventilation test accounted for the lack of observed ST T changes

Case 7 A 46 year-old male accountant was hospitalized 18 months prior to our evaluation with a diagnosis of coronary insufficiency after experiencing sharp midsternal pain radiating to the back He returned to work one month later and remained physically active participating in water and snow skiing as well as bicycle riding without difficulty Throughout this time however he continued to experience episodes of dull, aching retrosternal discomfort, occurring during emotional stress but unrelated to exertion and not relieved by nitroglycerine On admission to this unit, physical examination, laboratory data, and an ECG were unremarkable (Fig 7A) Prior to TM testing a 60 second period of hyperventilation produced ST segment flattening with a biphasic T wave at a heart rate of 100 beats per minute (Fig 7B) The TM test produced more remarkable segmental ST depression at a comparable heart rate (Fig 7C) Because of the patient's young age atypical chest pain and equivocal treadmill stress test coronary arteriography was performed and demonstrated normal coronary vessels.

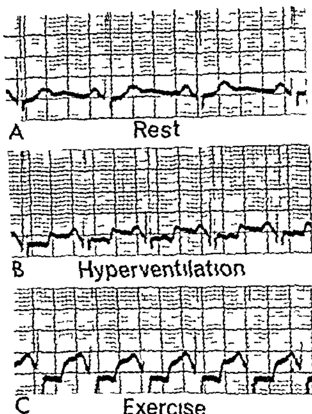


Fig 7 A through C *A* Resting electrocardiogram demonstrates no abnormalities *B*, Hyperventilation produces ST segment depression after 60 seconds *C* Exercise testing is accompanied by J point depression as well as by further depression of the ST segment. The test was interpreted as inconclusive

Discussion

Our case reports illustrate that hyperventilation alone may be responsible for a false positive exercise test in our series this occurred with a significantly greater frequency in patients whose coronary arteriograms were normal (15 per cent) than in those with demonstrable coronary vascular obstruction (3 per cent) Ischemic appearing hyperventilation changes were the only source of false positive stress test interpretation in our series all other patients free of coronary disease had negative hyperventilation and TM tests

Hyperventilation is known to be associated with ECG changes in persons without apparent heart disease[4,9,11,14] their incidence has been

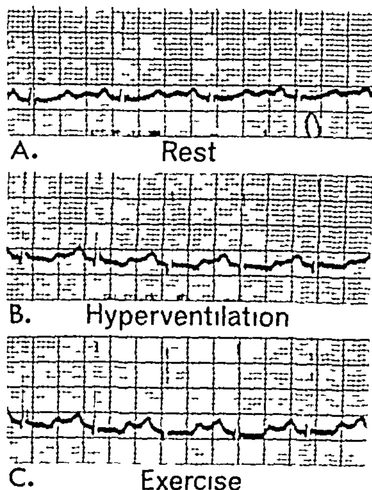


Fig 5 A through C *A* Resting electrocardiogram prior to treadmill testing shows only minor ST T abnormalities *B* During hyperventilation heart rate 110 per minute some downsloping of the ST segment is present *C* At a similar heart rate during exercise stress the downsloping ST segment is accompanied by J point depression The exercise test was interpreted as showing equivocal evidence of ischemia

seconds produced marked RST abnormalities (Figs 3*A* and 3*B*) Inasmuch as such abnormalities precluded valid interpretation of subsequent stress ST changes the precordial lead was moved medially a repeat hyperventilation test showed no abnormalities During exercise using the repositioned lead the patient reached Stage V attained a heart rate of 170 per minute (Fig 3*C*) and demonstrated no evidence of myocardial ischemia In view of the negative exercise test a recent prior normal coronary arteriogram and absence of symptoms repeat angiography was not recommended the patient was reassured that evidence of coronary artery disease was lacking

Case 4 A 47 year old housekeeper with a history of hypertension for many years first experienced knife like chest pain at age 42 Her pain occasionally radiated to the neck and base of the tongue The pain was nonexertional occurring primarily at night but was relieved by sublingual nitroglycerine Some episodes of chest pain had been associated with ECG abnormalities the nature of which were not disclosed to the patient During one hospital admission for evaluation of pain she was treated with steroid medication for myopericarditis with alleged prompt resolution of both pain and ECG changes on another admission myocardial

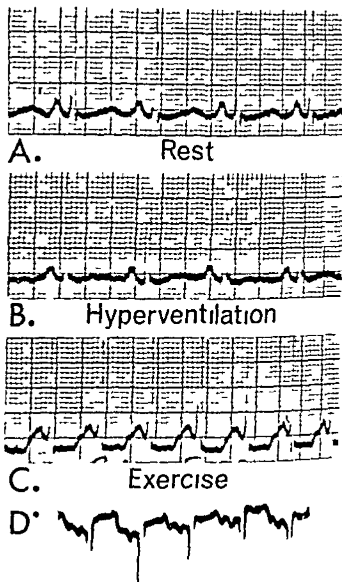


Fig 6 A through D *A* Baseline electrocardiogram *B* Hyperventilation to heart rate 95 per minute produces no changes *C* During exercise at heart rate of 150 per minute J point and ST segment depression occur during chest discomfort *D* Hyperventilation occuring spontaneously during cardiac catheterization A heart rate of 145 per minute is achieved At this heart rate significant J point and ST segment depression with T wave inversion occur

infarction was considered but could not be documented Except for these intervening episodes the patient s effort tolerance was normal With the exception of a blood pressure of 152/100 physical examination and laboratory data were normal The resting ECG showed nondiagnostic ST segment flattening in the inferolateral leads (Fig 4*A*)

mented coronary artery disease it must be stated that such changes do not exclude the possibility that myocardial ischemia is present. Reports of ischemic heart disease corroborated by enzyme elevation and abnormal ECG s in patients with normal coronary angiograms [20-23] as well as those instances of documented myocardial infarction in patients who later are found to have normal coronary arteriograms [24-27] are pertinent in this regard. Others[28,29] have shown that increasing heart rate by cardiac pacing can result in myocardial lactate production in patients with chest pain and normal coronary arteriograms The available evidence therefore suggests that ischemic heart disease in the absence of angiographically demonstrable obstructive coronary artery disease exists. The mechanisms responsible for the myocardial ischemia in these situations remain unexplained, but could be operating in our patients who exhibit ischemic appearing RST changes during hyperventilation In this regard it is of interest that in three of our cases (Nos. 2 4 and 7) the degree of ST depression during exercise was more pronounced than during hyperventilation

Valid interpretation of exercise stress tests in individuals who demonstrate ischemic appearing RST segmental depression during hyperventilation is extremely difficult. At the present time we believe that these represent false positive exercise tests and that hyperventilatory ECG alterations are the most common bases for false positive responses to TM testing In view of the foregoing discussion and the fact that some patients have such hyperventilatory changes in the presence of abnormal coronary arteriograms however we are alert to the possibility that some form of ischemic heart disease is not excluded. The routine practice of hyperventilation prior to exercise testing is encouraged, with subsequent interpretation of stress tests in light of the response to hyperventilation

Summary

In a series of 238 patients having hyperventilation tests just prior to treadmill exercise and selective coronary arteriography during the same hospital admission 15 per cent of 46 patients with normal coronary vessels had electrocardiographic changes during hyperventilation that were virtually identical to those of myocardial ischemia The hyperventilatory ECG changes were the sole basis for false positive interpretation of their stress tests. Patients with normal coronary angiograms who had no ECG alterations during hyperventilation all had negative treadmill tests

In contrast only 3 per cent of 192 patients with angiographically demonstrable coronary disease had ischemic changes during hyperventilation Awareness that not all RST alterations seen during hyperventilation are easily distinguishable from those due to myocardial ischemia is of the utmost importance in evaluating treadmill tests as errors in interpretation may thus be minimized resulting in fewer false positive readings

Although the number of patients is small we found that ischemic ECG changes seen during hyperventilation (as well as during exercise) in patients with suspicious histories indicate that very probably no coronary artery disease exists The routine performance of adequate hyperventilation testing prior to exercise is strongly urged.

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reported to be as high as 73 per cent.[15] The ECG alterations usually observed are production or accentuation of nondiagnostic T wave inversion, although ST segment depression, not usually mistaken for myocardial ischemia has occasionally been seen [4,9,10,14,15] In our cases, we found that ST segment changes were rather pronounced and resembled *ischemic* ST depression

During the period of the RST inverval ventricular repolarization is occurring Normally repolarization does not displace the RST segment from the isoelectric baseline However, under certain abnormal conditions such as ischemia, ventricular hypertrophy, digitalis administration or electrolyte disturbances the sequence and/or rate of repolarization in different areas of myocardium is altered resulting in deviation of the RST segment and T wave vectors [12]

The mechanisms by which hyperventilation alters the repolarization process have not been clarified Proposed explanations include change in heart position respiratory alkalosis alteration in potassium balance autonomic stimulation (either beta adrenergic or parasympathetic) and tachycardia

Change in heart position As electrocardiographic changes similar to those seen in hyperventilation have been seen during assumption of erect or lateral recumbent positions it was postulated[12,13,15] that diaphragmatic movements during hyperventilation so altered the position of the heart as to explain at least in part the ECG changes Kemp and Ellestad [12] however, showed that the ECG abnormalities that occur on standing gradually revert to normal, whereas those that occur during hyperventilation persist throughout the hyperventilation period

Respiratory alkalosis Electrocardiographic alterations associated with alkalosis consist of T wave flattening or inversion and QT prolongation [17] Biberman and colleagues[15] have excluded respiratory alkalosis as a causative mechanism of hyperventilatory ECG changes by demonstrating that hyperventilation into a closed system results in ECG changes in the absence of concomitant alterations in arterial pH or PCO_2 In addition, these investigators found no correlation between quantitive pH changes and alteration of the T wave configuration

Potassium flux Transient rises in extracellular potassium may accompany the early phases of hyperventilation,[18] thus possibly bearing a relationship to the observed ST T wave changes. On the other hand Thompsen and colleagues[19] found that potassium loading could prevent the T wave changes seen during hyperventilation Biberman and co workers[15] were unable to confirm significant plasma potassium fluxes during 60 seconds of hyperventilation even though ECG changes did occur they concluded that altered extracellular potassium could not be responsible for the ECG changes Similar conclusions were reached regarding possible contributory roles of plasma sodium calcium and magnesium [15]

Autonomic neural activity Autonomic nervous system activity probably plays a contributing role in hyperventilation ST changes the effects of pharmacologic interventions are unpredictable Vagal blockade with propantheline bromide has been shown to reverse resting RST abnormalities seen in anxious young men and to prevent the exaggeration of these changes during hyperventilation[9] however accentuation of ST segment shifts by administration of atropine has also been reported [16] Beta adrenergic stimulation with isoproterenol has been shown to produce RST segment and T wave changes[15] intravenous propranolol has reportedly *attenuated* or abolished such changes [16] Epinephrine may produce resting ECG changes identical to those seen in the same individuals during hyperventilation [10]

It is possible that adrenergic stimulation either by administration of exogenous sympathomimetic agents or by endogenous catecholamine release occurring during hyperventilation leads to asynchronous myocardial repolarization How this occurs is unclear but one might postulate that heterogeneity of vasoconstriction or vasodilation as well as disparate neural innervation in the different layers of the myocardium lead to abnormalities of repolarization

It is commonly believed that the RST changes produced during hyperventilation have a distinctly different configuration from those due to ischemia [12] Our cases and others[11,14] illustrate that the ST depression may closely resemble that seen in myocardial hypoxia Inasmuch as we have seen albeit less frequently, similar hyperventilatory changes in patients with docu

Current concepts of therapy with digitalis glycosides Part II

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The use of digitalis preparations in ischemic heart diseases

The role of digitalis therapy after acute myocardial infarction is uncertain [8] Nearly one half of patients with acute myocardial infarction have congestive heart failure usually of a mild nature Severe heart failure or pulmonary edema occurs in approximately 12 per cent of patients with acute myocardial infarction In the face of myocardial infarction digitalis may improve myocardial contractility However during the first few days after an acute myocardial infarction patients in mild congestive heart failure do not appear to improve their cardiac output significantly with digitalis [29] In fact in some patients digitalis may cause a rise in systemic vascular resistance prior to its inotropic effect leading to an increase in the energy demands on the heart and a fall in cardiac output Also it has been shown in experimental animals that increasing the inotropic state with digitalis may cause enlargement of the developing infarction On the other hand, when failure is due to a tachyarrhythmia that can be controlled by digitalis, use of the drug is probably beneficial

Studies in experimental animals appear to demonstrate a lower threshold and longer duration for toxicity with digitalis glycosides during the three to five day period after an acute myocardial infarction [30] As might be expected, the distribution of H^3 digoxin in the infarcted canine left ventricle is altered This may predispose to electrical instability in the heart Whether this increased sensitivity to digitalis occurs in humans with myocardial infarction given therapeutic doses of digoxin remains controversial [31]

Evaluation of left ventricular performance in patients free of congestive failure convalescing from acute myocardial infarction indicates that although digitalis may improve indices of left ventricular function improvements in resting cardiac index or systemic vascular resistance are not consistently observed.[32] It is possible that during exercise cardiac output responses would be improved but this point must be examined more critically

Therefore in patients with acute myocardial infarction and mild congestive failure digitalis is not the primary choice of therapy However in patients with severe failure and/or arrhythmias ordinarily responsive to digitalis the drug should be employed. In these patients it would seem prudent to use somewhat lower doses and slower rates of digitalization than usual

In cardiogenic shock digitalis glycosides improve indices of myocardial contractility and ventricular function in some patients However the response is variable and there does not appear to be any increase in survival with the use of digitalis in cardiogenic shock [33]

If the heart is markedly dilated in either myocardial infarction or cardiogenic shock a positive inotropic agent such as digitalis should decrease ventricular size and increase cardiac efficiency This theoretical proposition has been difficult to translate into increased patient survival

It is frequently stated that patients with severe angina pectoris particularly those with angina

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Although acidosis has been mentioned as a possible factor in digitalis toxicity its role is unclear

Alkalosis does not appear to change the myocardial toxic threshold for digitalis However once toxicity occurs alkalosis delays its reversal

Hypothyroidism results in increased sensitivity to digitalis Both therapeutic and toxic effects are found at lower doses Conversely as regards toxicity hyperthyroid patients are relatively resistant to digitalis.

There appears to be an increasing sensitivity to digitalis toxicity with advancing age In young persons large doses and high serum levels of the agent may be well tolerated, whereas in the elderly lower doses lead to toxic manifestations In the case of digoxin this may relate to the lowered glomerular filtration rate and decreased lean body mass with advancing age but also the myocardium per se seems to be more sensitive with advancing age

Other than renal insufficiency the most frequent cause of digitalis toxicity is diuresis and potassium and perhaps magnesium loss Toxicity precipitated in this manner is frequently associated with normal serum potassium levels and also with levels of digitalis that may be within the therapeutic range

The diagnosis of digitalis toxicity rests upon clinical grounds because if the condition needs to be treated, therapy will have to be instituted prior to the availability of a report on the digitalis blood level The history of digitalis intake administration of diuretics or other factors mentioned above that predispose to toxicity are most important Although atrial tachycardia with block bidirectional tachycardias and atrioventricular dissociation are considered to be characteristic of digitalis intoxication ventricular premature beats alone or in bursts and disturbances in atrioventricular conduction occur more commonly

Recent studies have indicated that salivary K^+ and/or Ca^{++} concentrations are significantly higher in patients with digitalis toxicity than in nontoxic patients receiving digitalis[41] The product of salivary Ca^{++} and K^+ concentrations was even more significant in separating out the digitalis toxic group Large scale studies with this technique have not been performed and it is doubtful that this technique will find wide clinical application

Treatment of digitalis toxicity

The first decision to be made once digitalis toxicity is diagnosed or suspected, is whether the manifestation is serious enough to warrant treatment Treatment is urgent only when the arrhythmia threatens life or disturbs the efficacy of the heart as a pump

Besides discontinuing the drug potassium administration in the presence of adequate renal output remains the standard and most effective method for treatment of toxic arrhythmias when atrioventricular conduction is normal In the presence of depressed atrioventricular conduction the use of potassium may be hazardous Ventricular irritability appears to relate to loss of intramyocardial potassium and therefore even in the face of normal serum potassium levels potassium administration will usually be effective

Other agents that have been used effectively in digitalis induced tachyarrhythmias have been propranolol diphenylhydantoin lidocaine, quinidine procainamide and bretylium tosylate Most of these act via their general anti arrhythmic mechanisms and have no specific anti digitalis actions Of these all except diphenylhydantoin lidocaine and bretylium tend to depress atrioventricular conduction Magnesium sulfate also successfully reverses toxicity especially when serum magnesium levels may be low

Propranolol and diphenylhydantoin have been reported to be particularly useful in the treatment of digitalis induced tachyarrhythmias

Most of the anti arrhythmic agents have some myocardial depressant properties and their beneficial effects as anti arrhythmics must be weighed against this factor Propranolol appears to be the most depressant agent in anti arrhythmic doses but is a highly effective agent. Practolol which is available in Europe appears to have less of a myocardial depressant effect but a potent negative chronotropic effect

decubitus may benefit from digitalis therapy In the absence of congestive heart failure, ouabain ameliorates the failure associated with exercise induced angina but does not appear to prevent the development of anginal pain [34,35] It has also been demonstrated that an increased central blood volume lowers, and a decreased blood volume raises the threshold for angina Thus if improved cardiac function results from digitalis therapy and causes a diuresis it should aid patients with the anginal syndrome However, quantitative studies are lacking in this area The majority of patients with angina do not have marked cardiomegaly and are not in cardiac failure Therefore it is unlikely that digitalis would have any great effect on this group, and in some patients through its positive inotropic action digitalis increases the energy demands of the heart and precipitates angina

When patients with angina have cardiomegaly or are in overt congestive heart failure, digitalis and diuretics will tend to reduce the filling pressures and volume of the heart, and therefore improve the energetic relationships In these circumstances digitalis therapy may ameliorate the anginal syndrome

The prophylactic use of digitalis[36]

It has been demonstrated in experimental animals that digitalis will retard the development of cardiac hypertrophy in the overloaded heart Also it has been noted that some patients with cardiac disease but without apparent cardiac failure develop less of an oxygen debt during exercise when they have been digitalized than when they have not been treated These observations have led some physicians to suggest that prophylactic digitalization may slow the progression of cardiac disease and may improve the patient s functional capacity However, the efficacy of such treatment has not been critically examined and the toxic potentials of digitalis suggest that caution be exercised until the benefits of prophylactic digitalization are more clearly defined

A special consideration of particular importance is the use of digitalis in patients with idiopathic hypertrophic subaortic stenosis In these patients the inotropic effect of digitalis may increase the ventricular outflow obstruction so that prophylactic digitalization may be contraindicated

Digitalis intoxication

It has been reported that up to 20 per cent of patients receiving digitalis admitted to some medical services have evidence of excessive digitalis dosage [37] Toxic manifestations of all digitalis preparations appear to be similar Since the inotropic effect of digitalis is related to its concentration, the force of contraction continues to increase up to the point of toxicity Therefore at high therapeutic levels the patient is very close to toxicity The serum levels of digoxin in patients with definite toxicity usually exceed 2 ng per milliliter Patients who are not toxic will also occasionally reach this range This overlap may be partially explained by factors that modify the sensitivity of the myocardium to the effects of cardiac glycosides [38] These include the electrolyte status ischemia, sympathetic support to the myocardium, and the status of the conducting system In certain conditions such as atrial fibrillation, the patients appear to be able to tolerate higher serum levels whereas when there is diffuse disease of the myocardium or the conducting system, lower than usual levels of digitalis may be associated with development of toxic signs

There are many factors that modify digitalis toxicity [39] Potassium deficiency will potentiate those toxic effects of digitalis that appear as tachyarrhythmias or ventricular irritability This may be seen even within usually non toxic ranges of serum and myocardial digitalis Hyperkalemia potentiates the inhibition of atrioventricular conduction by digitalis

Hypercalcemia potentiates the therapeutic and toxic effects of digitalis and in general calcium should not be administered to the digitalized patient

Hypomagnesemia also predisposes to digitalis toxicity and should be considered as a factor in digitalis induced arrhythmias particularly in conditions that lead to loss of Mg^{++} from the gastrointestinal tract or in the urine Cardiopulmonary bypass decreases serum Mg^{++} by diluting extracellular volume Hypomagnesemia has been reported to result in increased binding of digoxin to the myocardium The loss of myocardial K^{+} induced by digitalis which probably is partially responsible for arrhythmias is inhibited by Mg^{++} administration in experimental animals [40]

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Hypoxia lowers the toxic threshold for dig

most effective in restoring cardiac output and reversing congestive failure in low output states *secondary* to hemodynamic overload of the myocardium such as in hypertensive or rheumatic valve disease with left ventricular failure Digitalis is relatively ineffective in high output failure seen with thyrotoxicosis anemia, arteriovenous fistulas beriberi heart disease and acute glomerulonephritis One would expect little if any benefit in patients with mitral stenosis and sinus rhythm In general digitalis is useful in patients with atrial fibrillation because of its depressant effects on atrioventricular conduction Patients with diffuse myocardial disease of any etiology often respond poorly to digitalis

Digitalis glycosides have the same positive inotropic effects on the failing right heart as on the left heart. However patients with cor pulmonale seem to have an increased propensity to digitalis toxicity particularly as manifested by atrial tachycardia with block It has been demonstrated that patients with cor pulmonale have essentially normal turnover times for digoxin [48] Thus it is postulated that acid base or electrolyte abnormalities and hypoxia may contribute to the apparent increased sensitivity of these patients to the toxic effects of digitalis

Hemodynamic studies in patients with chronic pulmonary disease and cor pulmonale reveal a variable response to digitalis In some patients with cor pulmonale cardiac output may fall after digitalization [49] Thus although digitalis is not contraindicated in cor pulmonale additional caution should be exercised when using this agent, and treatment of the underlying pulmonary disorder with correction of hypoxia remains of primary importance

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When digitalis causes severe depression of atrioventricular conduction with slow ventricular rates temporary ventricular pacing should be instituted In ventricular tachyarrhythmias when doses of anti arrhythmic agents must be administered that may suppress atrioventricular conduction, the combination of pacing and drugs should be employed Occasionally, if tachyarrhythmias fail to respond to anti arrhythmic agents they will respond to overdrive pacing

Digitalis markedly lowers the ventricular fibrillation threshold for electrical stimuli Therefore, cardioversion of sustained tachyarrhythmias due to digitalis is hazardous and should be avoided If the arrhythmia does not respond to drug therapy and threatens the patient s life, cardioversion may be attempted beginning at very low energy levels

In the absence of digitalis toxicity direct current electrical cardioversion is a useful tool in the management of supraventricular tachyarrhythmias However the presence of significant levels of digitalis at the time of electrical cardioversion is associated with an increased incidence of arrhythmias and conduction disturbances after administration of the electrical shock [42] Therefore it is prudent to discontinue digitalis administration for a short period prior to elective cardioversion

There are a few experimental methods that may become useful in the treatment of digitalis toxicity The first of these is the use of serum harvested from rabbits that have been injected with albumin bound digoxin In the presence of this antibody rich serum digoxin can be removed from the myocardium and digoxin toxicity reversed.[43] The applicability of this technique to man is unknown

Because digitoxin has a large enterohepatic circulation, resins that bind sterols (colestipol and cholestyramine) have been used to shorten the serum half life of this agent in humans Cholestyramine reduces the serum half life of orally administered tritiated digoxin in human subjects by 35 per cent [44] Since digitoxin generally has a prolonged toxic phase this mode of therapy may have great promise in some patients In one case binding agents have also been used successfully in a patient with digoxin toxicity

A variety of other agents have been reported to have potent anti arrhythmic effects in the face of digitalis toxicity These include diphenidol and poassium canrenoate The data on these agents are too preliminary at present to base useful conclusions upon them

The use of digitalis in renal failure

In the presence of renal failure many authorities prefer to avoid the use of those digitalis glycosides that depend upon renal mechanisms for excretion of the cardioactive compound [25] Other authors have successfully been able to predict the dose of digoxin that can be used in patients with stable levels of renal insufficiency from the creatinine clearance and known clearance rate for digoxin [45] When these calculations are made digoxin may be used safely In this situation serial digoxin blood levels may be helpful in establishing whether under or over digitalization are present

When patients undergo peritoneal or hemodialysis only minor amounts of digoxin are removed in the dialysate [46] However, sudden shifts in serum electrolyte concentrations particularly K^+ or Mg^{++} may precipitate arrhythmias of digitalis intoxication

The use of digitalis in patients undergoing cardiac surgery

The administration of digitalis is frequently discontinued for a few days prior to cardiac surgery The rationale for this is to minimize the possible occurrence of digitalis induced arrhythmias at the time of myocardial hypoxia or when electrolyte shifts occur

During cardiopulmonary bypass there is a slight fall in the serum digoxin level that probably is due to a dilutional effect caused by transfusions and addition of pump priming fluid [47] However, since the majority of the digoxin in the body is bound to tissues the total loss of digoxin during a cardiopulmonary procedure bypass is relatively slight

In the first few days after surgery when there may be diminished renal function the excretion of digoxin is reduced so that the maintenance requirement will be less than usual

Clinical use of digitalis

The clinical usefulness of digitalis varies with the etiology of the heart disease the rhythm disturbance present and the presence or absence of specific valvular lesions In general digitalis is

Annotations

Of one doctor

The trends toward specialization and over specialization make it difficult or even impossible for a patient to identify or even have a responsible private doctor Many patients now go to buildings institutions, clinics or groups but not to a doctor The history and physical examination are too frequently obtained by a doctor in training out of the medical school only a year or two or even not yet graduated. Consultants are engaged freely each without a sense or feeling of full responsibility for the patient. The patient belongs to the building institution, or group One doctor may be head of a "committee of doctors in his section but on weekends holidays or vacations even the chairman of the committee is off duty Thus, during these periods and at night the patient becomes the patient of another doctor who is not fully acquainted with his illness data, and therapy and who displays little sense of responsiblity for the total care of the patient Nevertheless being on duty at the time this doctor makes diagnostic and therapeutic decisions of importance often drastic The intentions are good, but the personal responsibility for proper motivation in management is lacking In short, too many patients are treated by committee Furthermore referrals to specialists must be kept among the members of the "closed group or committee regardless of ability However the private physician can send his patient with impunity to the best consultant available and from anywhere in the world.

Patients and their families need one private doctor not a committee This doctor assumes full responsibility for all medical decisions and the consequences The patient then knows to whom to go for advice and the solution of medical problems The maturity and ability of the physician are known. A close doctor patient relationship develops and the patient knows who his doctor is and also understands the role and responsibility of any consultants employed.

Every person or family needs one doctor not an institution or building for the best and most satisfying medical care

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Physicians and medical electronic equipment A critical review of our modus operandi

Modern technology has profoundly affected the practice of medicine It has enhanced the quality of medical care but against this its implementation has brought about new complexities in procurement management and operation These complexities have been created primarily by the growth of the medical industry and the expansion of the consumer market that now ranges from large medical centers and community hospitals to practitioners offices

At this juncture the physician has been called to assume new responsibilities, to manage and operate complex hardware to understand the intricacy of the electronics and, based upon medical and managerial judgement decide on the purchase of equipment, define specifications system operations etc It is pertinent therefore to ask if the current generation of cardiologists and physicians at large are qualified to undertake this responsibility and if current trainees are being prepared to do so in the future

In a time of spiraling cost of health care delivery when federal support to sponsored programs is being curtailed and when the consumer the federal government and insurance carriers are in search of ways to decelerate this inflationary process it is pertinent for our profession to assess our role in the control of this growing technology our efficiency in exerting this control and then search for methods to transform the system into a more efficient operation. Some of the questions we should ask ourselves in this regard are

1 Where did we gain the expertise to evoke complex technical decisions?

2 Do we have the knowledge required to evaluate in a critical manner the systems we purchase?

3 If problems exist, what actions are we taking to remedy them?

Let us analyze each of these questions separately In the majority of cases physicians expertise in these technical matters is the product of growth through trial and error and in only few instances does it result from a formal education in electronics or engineering directly applicable to the problems they need to solve Although this method has appeared

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involved, the software configurations to meet these requirements The engineering members may also be able to help in establishing our operational requirements if they know what hardware and software are available and what these components can do

University centers that have consistently provided leadership in the development of new medical practices should be the first to implement this approach in an organized, coordinated fashion making the services of this team available to the community to prevent repeated occurrences of the problems we have discussed

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Clinical problems associated with the variable biologic availability of digoxin

Treatment with any of the cardiac glycosides requires care and caution. The response of individual patients is not predictable and since the time of Withering physicians have been taught to titrate the daily dosage to each patient's needs The ratio between toxic and effective doses is often low In these circumstances it is highly desirable that preparations of the glycosides should be consistent in potency In the last two years it has become clear that tablets of digoxin used in many countries of the world are far from equivalent in their potency [1-6] It was the introduction of sensitive and accurate methods for assay of plasma digoxin concentrations which brought this problem to light but it has almost certainly existed for many years

The clinical problem lies with the fact that a digoxin tablet may contain the correct dose of the drug but provide only a portion of this dose for absorption by the patient i e there is a low biologic availability of the digoxin dose When digoxin is administered orally as a solution absorption is nearly complete [7] Incomplete absorption occurs if a digoxin tablet dissolves very slowly in the gastrointestinal fluids It appears that the capacity to absorb digoxin is then limited by the gastrointestinal transit time The dissolution rate of digoxin tablets marketed in the United States and Britain varies considerably from brand to brand and some brands vary widely from batch to batch.[6,8] This variation in dissolution rate leads to marked differences in the plasma digoxin levels and clinical response achieved during maintenance digoxin therapy [6,9,10] Table I shows the mean digoxin levels recorded in 19 patients Each had used four different brands of digoxin at the same daily dosage Levels with brand A are 35 per cent higher than those obtained with brand D Some patients are markedly sensitive to differences in the dissolution rate of the tablets and with them the changes in digoxin level are even more startling (Fig 1) Until recently over half the British patients using digoxin received Lanoxin (Burroughs Wellcome) Even with this the longest established brand, there have been formulation difficulties. Fig 2 shows the changes in the plasma digoxin levels achieved with Lanoxin during recent years.[11,12] These differences have resulted from modifications at first thought unimportant made in the manufacturing process at the end of 1969 and in May 1972

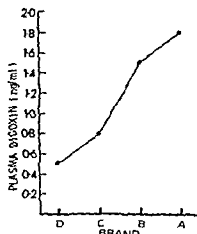


Fig 1 Plasma digoxin levels recorded in patient M W during use of brands A B C and D Digoxin dose was 0 5 mg per day

The basis of the differences in the dissolution rate and efficacy of the tablets appears to be the size of the digoxin particles In the United Kingdom powders of pure digoxin used for tablet manufacture have a geometric mean particle diameter of over 20 microns Digoxin powders of this large size dissolve slowly and are very poorly absorbed.[13] Tablets of high bioavailability are obtained from such powders only when the manufacturing method produces a reduction in digoxin particle size

The variation in the bioavailability of digoxin results in two types of clinical problem Standard dosages of slowly dissolving tablets may fail to produce a clinical response since ineffective digoxin levels are achieved If continued on such tablets the patient remains underdigitalized If the dosage is increased until a satisfactory response is obtained then dosages of 2 5 mg per day or more may be required, in this

successful it is not possible to determine if a different approach encompassing for instance a team of physicians engineers would have provided more efficacious results

Concerning our knowledge to evaluate the systems we purchase this assessment should start before the purchase order and involve primarily need cost effectiveness equipment efficiency backup procedures safety and maintenance

On the subjects of need and cost effectiveness we must consider the economics of the application and if we are putting our own funds where they can do the most good Thus the question of whether the method of payment is to be derived from patient service or as a direct overhead item increasing total operational cost is an important one In certain areas such as direct lifesaving equipment expense is less important and the cost can be accepted as a real fact of improving the quality of medical care However in many other areas serious doubt can be raised about a real need. Thus the justification for purchasing catheterization laboratory equipment that will be used once or twice a week and where the patient will have to bear directly or indirectly the cost is a moot point In these areas a cost analysis should definitely be performed to ascertain that this new approach will not unnecessarily increase the cost while only marginally improving care or just compete with a neighboring institution Through a regional utilization of resources the unnecessary overlap of expensive items can be avoided decreasing operational cost.

It is pertinent to ask whether when we purchase equipment its efficiency has been evaluated carefully After requirements and specifications are well delineated selection of a specific vendor should be made after factual information concerning past performance equipment design engineering and quality workmanship has been duly investigated Regarding the matter of backup procedures presumably we should at least have a system analysis done to determine the backup procedures necessary to allow some continuance of service in the event of a breakdown This is of the utmost importance in areas of critical care where the primary justification for the equipment is its permanent availability with 24 hour service provided Standby equipment should be available in the areas of patient monitoring to avoid single point failure leading to total system blackout

On the subject of safety it is necessary to analyze that neither the equipment nor the system in which the equipment operates can generate hazardous currents in the event of a malfunction Means for verifying equipment performance should be provided considering that an incorrect readout due to misalignment can itself establish a critical situation jeopardizing patient safety

Regarding maintenance the equipment should be analyzed to see that the quality of workmanship and layout are such as to provide a high mean time between failures and when failures do occur that the technicians can get inside to determine the cause of the failure Vendors frequently rely on independent service organizations and one important consideration is their ability to provide service under contract in a predetermined period of time Failure to do so results in prolonged down time that is extremely costly by virtue of idle personnel and hardware Although awareness of these subjects has increased and the Intersociety Committee on Heart Disease Resources has described these problems and proposed some solutions they have not been fully and widely implemented

If we all perform an inner search and self critique in most cases we may have to admit that we do not always consider these points we do not have analyses conducted before the equipment is purchased and we frequently have to live with our errors Furthermore we may ask ourselves Are we training the new generation of specialists to be qualified to assume this role? It is probably fair to say that in the majority of training centers this subject is not touched on in any formal manner What corrective steps could be taken to improve our current modus operandi?

Two clearly definable solutions that can provide the physician with sound guidance from a medical engineering and managerial point of view are (1) education of medical groups and (2) development of clinical engineering teams

Regarding the education of medical groups numerous postgraduate courses are currently offered The various professional organizations however have placed a negligible effort in the formal education of physicians in the technical and economical problems associated with purchase operation and maintenance of equipment It would be useful for the various associations to sponsor postgraduate courses in these areas The faculty composed of medical experts biomedical engineers and electronic engineers could provide an in depth discussion of various areas of equipment utilized. These organizations should also encourage the development of users groups which should meet at regular intervals, probably during national conventions These groups of individuals sharing common interests and problems would discuss various operational techniques, suggestions for improvement in design etc together with members of duly organized committees and manufacturing representatives.

Concerning the development of clinical engineering teams, the concept of clinical engineering has been advocated for some time but recent surveys indicate that only 300 are currently employed in U S hospitals.

Perhaps this small representation is due to the supposition that engineers cannot appreciate medical problems and hence physicians with some engineering training can make better clinical engineers than engineers with some medical training Perhaps we are reluctant to go outside our profession to seek advice in engineering type areas directly related to the way we are going to practice medicine

However we must face facts Our modus operandi is such that neither do we have the time nor the inclination for long term planning analyses and studies on equipment operation On the other hand the clinical engineer s approach is to anticipate and avoid crises He will most probably have received his training in the industrial environment where errors in design can affect whole product lines consequently his work is largely oriented around preventing problems.

Thus a mutually beneficial valuable interface exists The question therefore is to find a means for it to be utilized, to find a way where each side of the team can without conflicting responsibilities exercise their expertise The physician members of the team should be responsible for specifying the operational requirements what the equipment should do and how the people will be operating it The engineering members should specify the hardware and if computers are

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To diet or not to diet and what diet?

Perhaps in no area of research in the past ten years has there been a greater accumulation of data than in the area of coronary heart disease Particular attention has been paid to the role of blood lipids in this problem since this parameter lends itself to correction by both drug and dietary measures and in numerable epidemiological studies strongly suggest that persons with lower levels have habitually less coronary heart disease than those with higher levels. One can quite properly argue that the issue of the benefit to be derived from lowering lipids by drug therapy is still unsettled but within the next few years the results of the cooperative postcoronary drug study here in the United States and the primary study with clofibrate in Europe should help tremendously to clarify this issue

The matter of dietary management of blood lipids is somewhat different however there having been a somewhat greater and certainly a longer period of data collection for beneficial lipid changes and for associated improvement in morbidity and mortality rates while evaluating any potentially toxic side effects of such diets Our own ten year study of younger men with proved coronary heart disease[1] showed that after weight reduction, using a 28 per cent fat diet containing less than 9 per cent of calories as saturated fat and less than 400 mg of exogenous cholesterol daily was one method of first lowering blood lipids and second of significantly improving morbidity and mortality rates from subsequent coronary episodes In this study because of the restricted fat and exogenous cholesterol the degree of unsaturation of the diet did not appear to influence either serum lipid values or mortality rates Also the greatest benefit was derived by the younger under 45 age group suggesting early dietary change when needed. Because of the considerable fat restriction, dietary adherence was always difficult and required constant urging and support to achieve success throughout the entire period of the study

On the other hand, studies by Miettenen and associates,[2] Leren,[3] and Dayton and associates[4] achieved beneficial cardiovascular effects by improving blood lipids with the addition of considerable amounts of polyunsaturated fat to the usual dietary pattern, this being both palatable and readily acceptable by the volunteers One fact emerged from the Pearce and Dayton study[5] which was somewhat alarming and required careful evaluation Despite improvement in cardiovascular death rates the total mortality rate in the older cohort was similar and the noncardiovascular deaths were largely those of patients dying of carcinoma in the polyunsaturated group To add further anxiety Pinckney[6] in a recent editorial in this JOURNAL associated not only increased cancer incidence with increased polyunsaturates but from his preliminary observations also premature aging of the skin. Fortunately a careful review of the cancer incidence of a number of other field trials using highly unsaturated diets was done by Ederer and associates[7] and showed that polyunsaturate usage did not increase the incidence of carcinoma Hopefully this concept will now be laid to rest In addition evidence is now emerging[8] that polyunsaturated linoleic acid has a pronounced and significant effect on reducing platelet aggregation in man and this effect may be aiding importantly in reducing the reported incidence of ischemic heart disease in these studies through beneficial alteration of the clotting process This obviously should encourage its further utilization.

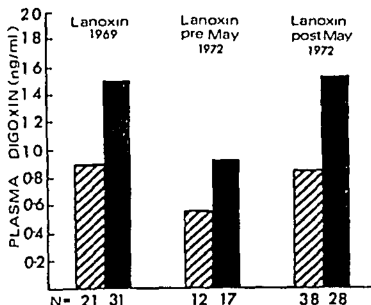


Fig 2 Mean plasma digoxin levels recorded in patients using Lanoxin at daily doses of 0 25 to 0 375 mg (striped boxes) and 0 5 mg (black boxes) All patients had normal or near normal renal function The 1969 levels were recorded by Chamberlain and associates.[11]

Table I Mean plasma digoxin levels recorded in 19 patients during use of four brands of digoxin (0 25 mg tablet) at constant daily dosages

	Brand			
	A	B	C	D
Mean plasma digoxin level (ng/ml)	1 01	0 92	0 82	0 75

situation a patient is at great risk from digoxin toxicity if a future supply of tablets are of high bioavailability or if there is a change to parenteral administration Unless the physician is monitoring the digoxin levels his courage is likely to crack before such adventurous dosages are reached However a similar problem exists for patients of low body weight or renal impairment for whom a daily dose of 0 5 or 0 75 mg per day of well absorbed tablets would be inappropriately high

Recent studies have revealed three other ways in which the biologic availability of digoxin can be reduced in special circumstances (1) Patients with certain types of intestinal malabsorption absorb the drug poorly[14] (2) Digoxin may be bound by other substances in the bowel lumen and made unavailable for absorption Maalox Kaopectate and charcoal have been found to produce this effect[15 16] (3) Drugs such as propantheline and metoclopramide cause an increase and decrease respectively in digoxin absorption due to altered gastrointestinal motility[17] Changes are marked if slowly dissolving tablets have been used but propantheline caused little change with digoxin solution and rapidly dissolving tablets.[18]

At present in the United Kingdom treatment with digoxin is made more hazardous by the existence of over 20 different brands of digoxin tablet, each with its own degree of bioavailability and with several brands variation from batch to batch Fortunately the in vitro measurement of tablet dissolution rate appears to be a valid means of predicting digoxin bioavailability and could be used to ensure equivalence of available brands In the United States the problem is slightly different from the British one Approximately 80 per cent of patients receive one brand (Lanoxin) which unlike the Lanoxin manufactured in Britain, has remained consistent The American Lanoxin has a dissolution rate of approximately 75 per cent in solution at two hours,[5 6] compared to the 90 per cent in 30 minutes of the current British Lanoxin.[8 10] Although the American Lanoxin is consistent in its efficacy the percentage of the dose absorbed, at present approximately 75 per cent of that which is obtained with a fluid preparation[7] could be increased if a faster dissolution rate were chosen Tablets which release more than 90 per cent of their dose in five minutes can be produced. An increase in the dissolution rate of the American Lanoxin would increase the plasma digoxin levels obtained with maintenance therapy and might improve the intersubject variation in digoxin levels found in a recent study[19] since slowly dissolving drug formulations tend to accentuate individual differences in absorption[20] A change in American Lanoxin would require a reassessment of each patient's digoxin dosage However the characteristics of very rapidly dissolving tablets are not yet fully known and they may be associated with new problems

These present digoxin problems will be lessened when new pharmacopeal standards are established Ideally the same standards should be used in all countries Improved precision and safety in digoxin treatment will result and discussion of the relative merits of digitoxin and digoxin can then begin anew

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Letters to the Editor

Experience with coronary artery bypass graft in community hospital

To the Editor

The experience of Dr Karnegis as reported in the July 1973 issue of the AMERICAN HEART JOURNAL is at such direct variance with ours at Saint John Hospital that a response is necessary

Saint John Hospital a community hospital of 501 beds began coronary artery bypass graft in October 1972 and the first 95 cases operated on here have resulted in only one death. This death was due to cerebral thrombosis on the third postoperative day A second death 34 days after surgery was due to a pulmonary embolus

All 95 cases were in the New York Heart Association class III or IV because of severe angina and were unable to carry out productive activity Age ranged from 31 to 66 (average age 53) there were 89 males and 6 females

Postoperative complications have been easily managed Postoperatively five of 21 patients who are under my care as the referring internist have had systolic time intervals pre and postoperatively and four of the five have manifested improved STI Three of the 21 patients have had pre and postoperative treadmill examinations and all three had improved systolic pressures and heart rate multiples

Surgery was performed on all 95 cases by the same surgeon, and a select team of anesthesiologists, cardiologists and cardiac nurses and this undoubtedly accounts for the excellent results this team approach has given our patients

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Reply

To the Editor

I am grateful to Dr Shors for his report

It is obvious that the future role of an experimental procedure depends on the appropriate analysis of dispassionately collected data There is simply no other way to approach in reality the consequences of the intervention.

As broader experience with the coronary artery bypass graft is accumulated we would do well to remember the lessons emphasized in Dr Spodick s[1] eloquent editorial

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REFERENCE

1 Spodick D H Revascularization of the heart—numerators in search of denominators (editorial) AM HEART J 81 149 1971

Cardioversion by precordial thumping in asystole and ventricular arrhythmias

To the Editor

At the present time many authors have reported successful cardioversion by precordial thumping in asystole and ventricular arrhythmias

Twenty five months ago I myself began to experience extrasystoles They came only at night after retiring They occurred frequently though irregularly for many weeks but were not felt every night

With this in mind the author decided to experiment with himself At first I resorted to thumping but soon began to use pulsating hot showers over the precordia for at least three minutes before retiring The shower head was open to its fullest extent to produce the greatest pressure I have not felt any recurrence of the extrasystoles

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What then should the practitioner of medicine do at this time? The bulk of evidence seems to show that dietary management of those susceptible to or already affected by coronary heart disease is beneficial and indicated. In addition, if it is to have the greatest effect, it should be started as early in life as possible. If the patient is well enough disciplined to severely restrict his fat and cholesterol intake (these are few in number) it may not be necessary to add polyunsaturated fats to the diet. However, for the large majority of patients who resist any major dietary changes, the substitution of polyunsaturated fatty acids for saturated ones in the diet is clearly indicated at this time so as to make some inroad into the persistantly high coronary heart disease rate found in the United States.

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The pathology of the heart By E G J Olsen M D New York, 1973 Intercontinental Medical Book Corporation, 224 pp $22 50

Dr Olsen s book on the pathology of the heart represents a condensed version of the morphologic changes produced by disease in the human heart. The extent of the condensation of the knowledge of cardiac pathology is readily appreciated when this 200 page volume is compared with the mul tivolume opus of Professor R Hudson Nevertheless clini cians students, interns and residents will find this book to contain a great deal of important information nicely con densed in these few pages All the common heart diseases congenital and acquired are discussed. The illustrations are good and the associated text is clearly and concisely written. For a quick and accurate review of cardiac pathology Olsen s book is highly recommended. The literature and more exten sive supplemental information can be found elsewhere Many good references are suggested by the selected bibliography included in Olsen s book

Effect of acute ischaem a on *myocardial function* By M F Oliver M D F R C P Lond. F R C P Ed. D G Julian, M.A M D F R C P Lond. F R C P Ed. F R A C P and K W Donald, D.S.C Q P M A M.D D.Sc F R C P Lond. F R.S.E. Baltimore 1972 The Williams & Wilkins Company 382 pp $19 25

The symposium on the effect of acute ischemia on myocar dial function was held in Edinburgh during May 1972 This book contains the papers and discussions which were pre sented at the meetings. The subject was rather extensively reviewed by the many participants. Among the major prob lems reviewed were models and methods for studying myocardial ischemia, effects of acute ischemia on myocardial cell structure function electrophysiology metabolism and performance and therapy in myocardial ischemia The dis cussions which followed each paper are most interesting as is usually so in symposia. The entire book is important It re flects the state of knowledge and interest in myocardial ischemia at the present time The presentations as usual in dicate the important gaps in knowledge and the difficulties in translating animal studies to clinical problems due to myocardial ischemia in man. This is an interesting and valuable book. The symposium must have been most valua ble to those who attended.

Book reviews

Electrocardiographic notebook Ed 4 By M Irene Ferrer M D Mt Kisco N Y 1973 Futura Publishing Company 154 pp $4 95

Dr Ferrer s nice little pocket size paperback notebook on electrocardiography continues to enjoy success This excellent presentation for beginners is fundamental in nature and easy to read The author has kept the discussion brief and up to date The tables diagrams and illustrations are well chosen Students and house staff as well as any beginners in electrocardiography will find this to be a very useful book

Electrocardiography By S G Owen M D Boston 1973 Little Brown & Company 180 pp $10 00

This small paperback volume on electrocardiography is intended for beginners. The text is designed for self teaching of concepts in electrocardiography and the interpretation of the recordings This is a simple clear and well planned manual The diagrams are well selected simple and clear This is not intended to teach all of electrocardiography The student must study other books and practice reading actual tracings as well Nevertheless this is a good book which will require thought in order to learn the principles of electrocardiography It is a useful small well planned manual

Heart disease in infancy Edited by Brian G Barratt Boyes John M Neutze M D Edward A Harris M D Baltimore 1972 The Williams & Wilkins Company 343 pp $28 00

This book contains the Proceedings of the Second International Symposium held in Auckland New Zealand during February 1972 The speakers were from New Zealand Australia and the United States of America all authorities in their respective fields The presentations are good and the problems discussed important ones e g diagnosis in the newborn profound hypothermia the common congenital anomalies postoperative care and genetics These are interesting clinically oriented papers The papers contain well selected bibliographies The discussions are especially interesting as they usually are at such symposia This is an excellent series of important papers which should interest all cardiologists The proceedings are highly recommended

Practical pediatric electrocardiography By Arthur J Moss, M D and George C Emmanouilides M D Philadelphia and Toronto 1973 J B Lippincott Company 148 pp $17 00

This manual consists of examples of common electrocardiograms encountered in the practice of pediatrics This is an addition to many practice manuals of similar format This one is different in that it is intended for pediatricians It is planned in a fashion similar to others already available for adult patients in that it consists of a series of tracings with a brief interpretations The examples of tracings are good and clear The reader will find this to be a useful addition to his library but it does not replace the need for a clear knowledge of the fundamental principles of electrocardiography

Pulmonary thromboembolism Edited by Kenneth M Moser M D and Myron Stein M D Chicago 1973 Year Book Medical Publishers Inc 355 pp

Moser and Stein edited this book on Pulmonary Thromboembolism based on a symposium held in La Jolla Calif during May 1971 This volume is concerned with pathogenesis experimental models pathology hemodynamic alterations diagnosis, and treatment of this important and common disease of man The many contributors and their respective papers summarize the problems related to thromboembolism very well This book should be of considerable value to undergraduate medical students as well as all physicians The contributors are among those most concerned with this disease Although it contains little that is new it is a valuable addition to the literature and an excellent source of information on current concepts of thromboembolism

Cardiology review By Jami G Shakibi M D and Philip R Liebson, M D Flushing N Y 1973 Medical Examination Publishing Co Inc 266 pp $10 00

This manual of cardiology review consists of 1 100 multiple choice questions similar in composition and purpose to those encountered in present day specialty board examinations The purpose of the book is to have the reader self assess his knowledge of cardiology through multiple choice questions The answer key is placed at the back of the book These 1 100 questions can help physicians prepare for the specialty board examinations in cardiology and internal medicine Students interns residents and trainees in cardiology will find this to be a useful book and a good timulus to the study of cardiology

Exercise testing and training in coronary heart disease Jean Marie R Detry M D Baltimore 1973 The Williams & Wilkins Co 79 pp $17 50

This 79 page paperback publication on exercise te ting and training in coronary heart disease summarizes in four chapters the state of knowledge of and interest in exercise in Europe and the United States of America The main subjects discussed are physiologic considerations exercise electrocardiography physical work capacity in coronary heart disease and physical training in coronary heart disease These chapters consist of 66 pages in English and a *two page* French conclusion The busy physician will find the manual to summarize briefly the important information on the subject This is not a critical review of this important subject however Dr Detry has brought together a great deal of the work on exercise and coronary heart disease in a concise manner This is well done but not a critical review of the many problems in exercise testing This book reveals the *extensive* lack of knowledge in this field. Industrial and insurance physicians will particularly find this to be a useful manual

American Heart Journal

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Editorial

Viruses and arteriosclerosis

George E. Burch, M.D.
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There is no evidence that establishes the fact that dietary intake of any type of food is the initiating cause of arteriosclerosis in man. The lesions seen at autopsy are scars— tombstones of previous pathologic processes. The calcified ulcerative lesions so common in the aorta of old people certainly represent the final manifestations of old chronic disease processes which were initiated many years earlier. The mechanisms for the initiation of the disease constitute an important problem. It has been my contention for some time that the *atherosclerotic* or arteriosclerotic plaques and streaks encountered in man represent a complex process in which the initiating injury remains unknown. Lipid and lipoprotein in the diet and in the blood stream of the high pressure vessels may be responsible for the type and amount of material which accumulates in the arterial lesions observed at autopsy. Nevertheless, there is no evidence that such substances in the diet initiate the lesions under ordinary conditions in average people. Furthermore, there are no data available yet to indicate why the lesions develop in the first place in specific sites in the high pressure blood vessels of the body. Intraluminal pressure must be an important factor[1] because the same blood also circulates through the low pressure vessels, such as the veins, but the lesions do not develop there. It is a disease of the arterial system, the high pressure vascular system.

Time must also be a factor in the development of the arteriosclerotic lesions noted clinically and at necropsy. Although the scars and old lesions are found in children and young people,[2,3] arteriosclerosis is a more extensive and fulminating disease in older people. The accumulation of calcium in any lesion, such as a hematoma, requires a considerable amount of time. This seems to apply also to the arteriosclerotic calcific lesions of the aorta and arteries. Initiating lesions for arteriosclerosis apparently begin in very early life, infancy and childhood, and the arteriosclerosis progresses as these early lesions repair and new ones form throughout life, which in turn also repair, resulting in plaques in varying stages of development regarded as atherosclerotic and arteriosclerotic. With aging, the progressive elevations in arterial blood pressure due to many factors, including physical and psychic stresses of life, along with the degeneration, hardening, and stiffening of the arteries due to aging processes, muscularis hypertrophy, and the ever developing arteriosclerotic plaques establish a vicious cycle as adulthood progresses.

Of most significance are the initiating factors, the first lesions of the vessels. It is true, were it possible to influence favorably the factors which influence repair, the extent of the resultant arteriosclerosis would be reduced. Certainly con

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Announcements

Asian Pediatric Congress

The First Asian Congress of Pediatrics under the sponsorship of the Philippine Pediatric Society Inc will be held at the Hotel Intercontinental Manila Philippines from April 30 through May 4 1974 The congress theme will be 'Towards Optimum Health for Asian Children Topics will include infectious diseases, community pediatrics neonatal pediatrics tuberculosis hemorrhagic fever neonatal problems parasitisms pediatric education diarrheas pediatric surgery preventive pediatrics and congenital anomalies. The official language of the Congress will be English Participating countries will include Australia Bangla desh Burma Hongkong India Indonesia Japan Khmer Republic (Cambodia) South Korea Laos Malaysia New Zealand Pakistan Republic of China Sri Langka (Ceylon) South Vietnam Singapore Thailand and the Republic of the Philippines Before March 31 1974 the registration fee for participants will be $30 U S funds and $15 U.S funds for guests After March 31 1974 fees will be $40 U.S funds for participants and $20 U S funds for guests Participants will be given daily luncheons and dinners on May 1 2 and 3 Accommodations at the Hotel Intercontinental will cost $13 50 (U S) for a single room or $17 50 (U.S) for a double room plus a 10 per cent service charge For further information regarding the congress please write Asian Congress of Pediatrics P O Box EA 100 Manila Philippines or Medical Center Manila Suite 506 1122 General Luna St Ermita Manila Philippines Tel 50 30 61 or cable Pediaphil

Radiology seminar

The twelfth annual seminar on Radiology in medical and surgical emergencies will be held March 23 to 30 1974 at the Playboy Plaza Hotel Miami Beach Fla This seminar is sponsored by the Department of Radiology University of Miami School of Medicine (at Jackson Memorial Hospital) Fees general $150 00 residents and fellows $75 00 For further information please contact Manuel Viamonte Jr M D Department of Radiology University of Miami School of Medicine P O Box 875 Biscayne Annex Miami Fla 33152

Pulmonary circulation symposium

The Czechoslovak Society for Respiratory Physiology and Pathology is organizing the Second International Symposium on Pulmonary Circulation sponsored by Societas Europaea Physiologiae Clinicae Respiratoriae to be held in Praha Czechoslovakia June 17 to 19 1974 Topics to be discussed include (1) long term development of pulmonary hypertension in chronic obstructive bronchopulmonary disease (2) pulmonary hypertension at high altitudes and (3) pulmonary circulation in left heart failure Preliminary application forms can be obtained from J E Purkyne The Czechoslovak Medical Society Sokolska 31 120 26 Praha 2 Czechoslovakia

Emergency 74

The Wisconsin Committee on Trauma of the American College of Surgeons will sponsor its Second Annual three day postgraduate course for nurses involved in emergency care Emergency '74 will be held April 17 18 and 19 1974 at the Pfister Hotel and Tower in Milwaukee Wis. The tuition of $75 00 includes text material all luncheons, and a reception

For further information contact Dr Joseph C Darin, 8700 W Wisconsin Ave Milwaukee Wis. 53226

Workshop in electrocardiology

The Rogers Heart Foundation announces the Thirteenth Workshop in Electrocardiology for cardiac nurses and interested physicians to be held at the Tides Hotel and Bath Club Redington Beach Florida on April 18 through April 22 1974 Program director will be Henry J L Marriott, M D and the workshop will be sponsored by the Rogers Heart Foundation and St Anthony s Hospital

For further information write Rogers Heart Foundation, St Anthony s Hospital St. Petersburg Fla 33705 or call (813) 894 0790

Rogers Heart Foundation Seminar

The Rogers Heart Foundation announces a seminar entitled 'The Phono and the Physical to be held at the St Petersburg Hilton hotel St. Petersburg Florida, on March 15 through 18 1974 The seminar of special interest to physicians and nurses, will be directed by Henry J L Marriott, M D and the faculty will comprise Horace T Castillo Rogers Heart Foundation Dieter Schwarzer President Schwarzer Company Framingham Mass. Bernard L Segal M D Hahnemann Medical College and Hospital Philadelphia Pa and David H Spodick, M.D Tufts University School of Medicine Lemuel Shattuck Hospital, Boston, Mass. For further details write Rogers Heart Foundation St. Anthony s Hospital St. Petersburg Fla. 33705 or call (813) 894 0790

adult man in the production of arteriosclerosis or even fatty streaks remains to be learned

When it is realized that fatty streaks are found in the aorta and arteries of young children without hypertension with little time for exposure to abnormal lipoproteins and even with normal lipid and lipoprotein levels in the blood it is evident that it is time to consider other factors which may be responsible for the accumulation of fatty streaks and arteriosclerosis. Our studies of young adults have revealed immunofluorescent antibody staining of antigen for Coxsackie virus in the aorta and arteries (Fig 1) Lipid bodies were found in the macrophages fibroblasts and smooth muscle cells (Fig 2) of the aorta of one of our young patients (19 years old) who died of a viral infection and in whom the aorta also displayed immunofluorescent antibody staining for Coxsackie B_4 virus The initiating cause and effect relationship of the viral infection to the accumulation of fat can only be conjectured but at the same time a possible relationship cannot be ignored. It is interesting that viruses (herpes virus) can stimulate cells even in tissue culture to produce cholesterol and fat[16] This supports some of our own studies with the Coxsackie virus in man in whom fat was found to accumulate in close proximity to Coxsackie B_4 viral antigen

Mice infected with Coxsackie B_1 and B_4 viruses and with encephalomyocarditis (EMC) virus revealed the presence of viral crystals (Fig 3) and immunofluorescent antibody staining in the aorta and large arteries It is quite possible that such viral infections could lead to damage of the vessels which with repair results in atherosclerotic or arteriosclerotic lesions Whether or not viral infections of the arterial vessels ultimately lead to arteriosclerosis is important and needs study Certainly viral infections of the arteries must have a deleterious effect on these vessels However the nature of the damage is still not clear This has not even been systematically investigated Surely there must be a broad spectrum of infectivity and degree of damage to the arteries by viral agents Acute arteritis phlebitis or vasculitis must be at one end of the spectrum and mild chronic to latent infection at the other These problems of viral infections (by slow viruses also) need careful study

We have found that the Coxsackie B_4 and EMC viruses will produce phlebitis in mice[13] Such viral infections of the veins may be responsible for some of the unexplained thrombophlebitis encountered in man Conditioning factors such as respiratory infection trauma surgery drugs malnutrition, toxic agents and many others could be responsible for the activation of dormant viruses or could predispose to viral infections of arteries and veins resulting in arteriosclerotic lesions (a repair state) local thrombosis, and thromboembolic phenomena Such conditioning factors could be important in the production of viral infections in arteries and all other blood vessels as well

Viral infections of the arteries in infants children and adults of both sexes need investigation among living patients, autopsy material, and experimental animals. The associated temporal roles of diet, blood pressure toxic agents and physical factors likewise require study Our investigations have produced a model which affords an opportunity to study these and other factors Because Coxsackie B_1 and B_4 and the EMC viruses form beautiful crystals and do infect arteries and veins they are particularly suitable for such experimental models The crystals of Coxsackie B_1 and EMC viruses can be detected readily in tissues under study by the electron microscope Thus not only can the presence of the virus be determined, but the precise location of the virus within each individual cell can be identified. Such observations are more direct than those made with the use of immunofluorescent antibody staining methods The latter can be of considerable assistance however

Several recent papers[2,3,17,19] have indicated possible factors which could initiate the lesions of arteriosclerosis in childhood Viruses and other infections and associated conditioning factors were not included or sufficiently emphasized in those reports Merely indicating that endothelial injury platelet sticking and adhesion endothelial proliferation and fibrin thrombus formation may be initiating causes of arteriosclerosis fails to establish why these phenomena develop in the first place Viral infections of the arteries could be an important fundamental etiologic factor resulting in platelet sticking localized fibrin thrombi and endothelial proliferation all of these being early responses to viral injury Conditioning factors could be important in predisposing to arterial viral infection

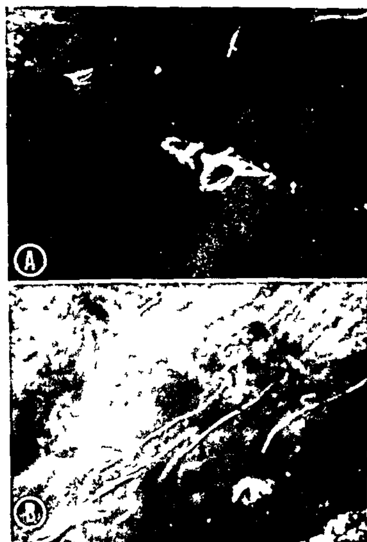


Fig 1 Immunofluorescent staining of Coxsackie B_4 viral antigen in cells of the adventitia of the aorta of a 19 year old man (×125)(From Burch G E Harb J M Hiramoto Y and Shewey L Viral infection of the aorta of man associated with early atherosclerotic changes AM HEART J 86 523 1973)

trol of arterial blood pressure diet, and habits of life need serious consideration Nevertheless, what are the factors which injure the arteries in the first place? Those who claim that arterial injury is unnecessary for atherosclerosis to develop have not yet established this contention in man and those who claim an initiating damage to the vascular wall is necessary also have yet to establish their claim Nevertheless arteriosclerosis is such an important and universal disease that at least some consideration must be given to new concepts and to the concept that initially some form of injury to the arterial wall is necessary, regardless of the cause or causes for the classical arteriosclerotic or late lesions scars or tombstones to develop

Recent reports[2,3] clearly indicate that lesions of the arteries exist in young children Studies of lipid patterns in young people and even of random infarcts are important in order to learn the possible role of lipid levels and complexes in the development of atherosclerosis. Unfortunately many investigators engaged in such types of studies seem to assume that lipids do produce atherosclerosis at the outset Such reasoning must be considered with extreme caution to avoid bias in any study or review of the literature Lack of consideration of other possible initiating causative factors could be an extremely important omission Just because mothers of newborn infants have a particular state of lipoproteinemia and other clinical manifestations said to be causally related to arteriosclerosis and because the cord blood sample of an offspring has a similar or related lipoprotein pattern these findings do not establish that lipoproteinemia has a cause and effect relationship to the development of arteriosclerosis Neither do such findings indicate that all important factors have been considered and properly eliminated. After all pregnant mothers and particularly newborn babies and children are extremely prone to viral infections especially of the upper respiratory tract Furthermore, suckling and young mammals (including man) are especially prone to infections with some of the most common viral agents known to infect and damage the cardiovascular and renal systems and the blood vessels[4,15] The picornaviruses for example are not only highly cardiotropic but they also infect and damage the blood vessels Infections with these viruses can be fulminating in very early life of man even in utero[5] It is during the very early life of man that he is least resistant to these viruses At this young age mortality and morbidity rates are extremely high

Viral infections in early life could be one of the most important initiating causes of vascular lesions which develop into arteriosclerotic lesions so well known in later adult life Fatty streaks in arteries are known to exist to varying extents in most infants and children[3] Some lead to only a little atherosclerosis in adult life whereas others result in marked atherosclerosis The fact that various members of the picornavirus group can infect and damage the arteries of man and other animals has been established by our own investigations[12,15] However, the precise role of these and other viruses (many yet unknown) which commonly infect infants children and

adult man in the production of arteriosclerosis or even fatty streaks remains to be learned

When it is realized that fatty streaks are found in the aorta and arteries of young children without hypertension with little time for exposure to abnormal lipoproteins and even with normal lipid and lipoprotein levels in the blood it is evident that it is time to consider other factors which may be responsible for the accumulation of fatty streaks and arteriosclerosis. Our studies of young adults have revealed immunofluorescent antibody staining of antigen for Coxsackie virus in the aorta and arteries (Fig 1) Lipid bodies were found in the macrophages fibroblasts and smooth muscle cells (Fig 2) of the aorta of one of our young patients (19 years old) who died of a viral infection and in whom the aorta also displayed immunofluorescent antibody staining for Coxsackie B_4 virus The initiating cause and effect relationship of the viral infection to the accumulation of fat can only be conjectured but at the same time a possible relationship cannot be ignored. It is interesting that viruses (herpes virus) can stimulate cells even in tissue culture to produce cholesterol and fat[16] This supports some of our own studies with the Coxsackie virus in man in whom fat was found to accumulate in close proximity to Coxsackie B_4 viral antigen

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Viral infections of the arteries in infants children and adults of both sexes need investigation among living patients autopsy material and experimental animals The associated temporal roles of diet blood pressure toxic agents and physical factors likewise require study Our investigations have produced a model which affords an opportunity to study these and other factors. Because Coxsackie B_1 and B_4 and the EMC viruses form beautiful crystals and do infect arteries and veins they are particularly suitable for such experimental models The crystals of Coxsackie B_1 and EMC viruses can be detected readily in tissues under study by the electron microscope Thus not only can the presence of the virus be determined but the precise location of the virus within each individual cell can be identified Such observations are more direct than those made with the use of immunofluorescent antibody staining methods The latter can be of considerable assistance however

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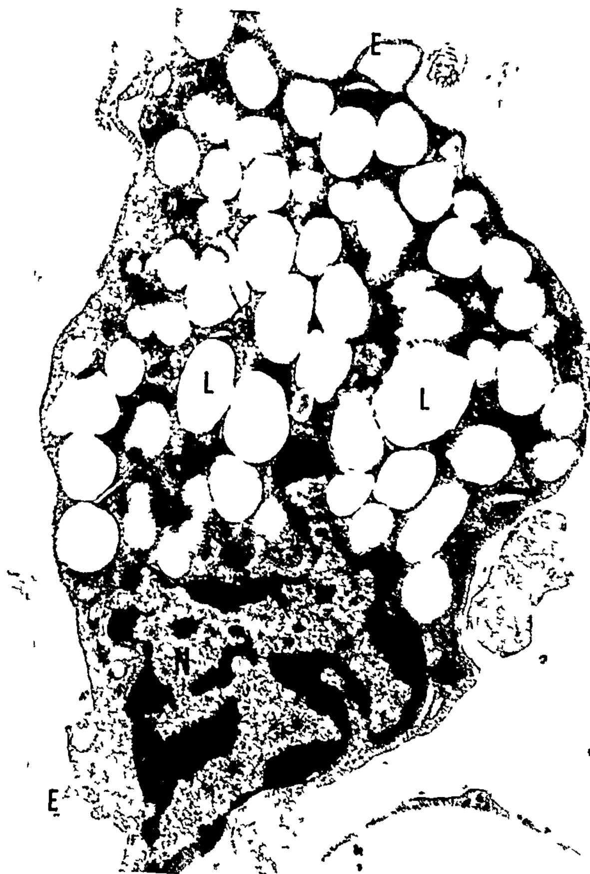


Fig 2 Electron micrograph of the intima of the aorta of the 19 year old man who had immunofluorescent evidence of Coxsackie B_4 virus in adventitial cells of the aorta (see Fig 1) Numerous lipid droplets (*L*) are contained within the cytoplasm of this macrophage The nucleus (*N*) is displaced to one side and thin protoplasmic extensions (*E*) protrude from the cell (×21 600) (From Burch G E Harb J M Hiramoto Y and Shewey L Viral infection of the aorta of man associated with early atherosclerotic changes AM HEART J 86 523 1973)

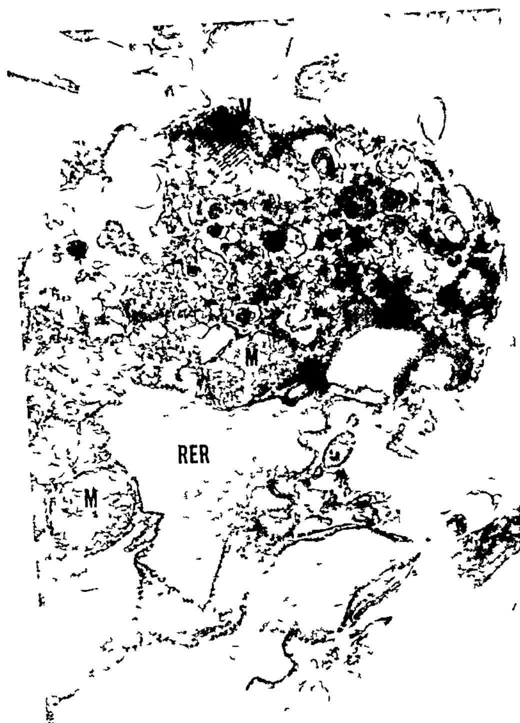


Fig 3 Electron micrograph of a fibroblast of the adventitia of the aorta of a newborn mouse infected with EMC virus A viral crystal (*V*) is located within an area of cytonecrosis characterized by membrane vesicle complexes and vacuoles The rough endoplasmic reticulum (*RER*) and mitochondria (*M*) are dilated. (× 38 400) (From Burch G E The etiology of arteriosclerosis—A thought AM. HEART J 83 434 1972)

and to the determination of the precise site where the viruses lodge, grow, and damage the vessels

Finally, this discussion hypothecates the possible role of viruses in the production of arteriosclerosis and thrombophlebitis Evidence for viral infections of the arteries and veins is accumulating with the precise role of such infections in the initiation of important common vascular diseases in man yet to be carefully investigated and determined In spite of the interest in diet lipid complexes smoking and other habits the incidence of deaths from arteriosclerosis and thromboembolic phenomena continues unabated in man Therefore, there is a need to introduce a new plausible idea to the research program

Viral infections are subject to control and prevention, both of which are extremely important additional considerations

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Clinical communications

Prediction of hemodynamic data in atrial septal defects of secundum type from simple and combined vectorcardiographic data

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Several successful efforts have recently been made to correlate electrocardiographic (ECG) and vectorcardiographic (VCG) data with hemo dynamic measurements in various cardiac lesions The correlations have generally been best in conditions with isolated pressure loads of one ventricle and less satisfactory in conditions with a dominant flow overload. There have been conflicting opinions on whether any useful ECG hemodynamic correlations exist at all in atrial septal defects [1-3]

We have recently reported that a substantially improved prediction of right ventricular systolic pressure (RVSP) from VCG data could be ob tained in isolated pulmonary stenosis by the use of combined VCG data selected by a multiple re gression analysis [4] This report describes a similar approach in 50 patients with atrial septal defects. The aims of the study were (1) to determine if simple VCG data are significantly correlated with hemodynamic measurements in atrial sep-tal defects, (2) to study the effect of flow and pressure on the ECG picture of right ventricular hypertrophy and (3) to explore whether the pre viously used statistical approach also improved the prediction of hemodynamic data in this com bined pressure flow overload state

Materials and methods

Patients Fifty patients with atrial septal defects of the secundum type were subjected to study In 36 patients the diagnosis has been con firmed later during operation the other 14 had hemodynamic findings typical for this lesion Only patients with atrial septal defect as their main cardiac lesion were included. Apart from this they were randomly selected. Two had in ad dition a moderate mitral insufficiency and one had moderate mitral and tricuspid insufficiency Two had atrial fibrillation A small valvular pulmonary stenosis of organic nature (gradient 35 mm Hg) could not be ruled out in one patient. In the others small right ventricular outflow tract gradients up to 30 mm. Hg were considered to be flow induced. One patient had biliary cir rhosis. Seven were taking digitalis at the time of the study

Since a widened QRS complex is an integral part of the ECG of atrial septal defects the pres ence or absence of a conduction disturbance may be difficult to establish from a criterion based solely on the QRS duration Therefore patients were admitted to the study irrespective of their QRS duration In nine this exceeded 0 11 sec the maximum value being 0 14 sec

The ages ranged from one to 60 years (mean 31 years)

Vectorcardiography VCG s were recorded by means of the axial lead system[5] as previously described,[4] using both high speed scalar and pho tographic planar recordings The recording equipment had a high frequency response (linear to 500 Hz) and input impedance (above 10 megaohm) The data were derived manually from these recordings a method involving errors not present in computerized interpretation The reproducibility of amplitude measurements seems however to be comparable with that of computerized Frank lead VCG s [6]

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Table I VCG data selected for correlation with hemodynamic data

- QRS duration
- QRS rotation in horizontal plane (CC = 1 figure-of eight = 2 C = 3)
- T rotation in horizontal plane (CC = 1 C = 2)
- QRS maximum and minimum in Leads X Y and Z
- Total forces oriented to the right left anterior and posterior (Σ Z− ΣZ+ Σ X− Σ X+) and their ratios
- X Y and Z of each 10 msec QRS vector up to 80 msec
- Maximal X Y and Z of P T and ST and their maximal spatial magnitude
- Maximal rightward anterior QRS deflection along the 135 degree axis in horizontal plane (Max RA)
- Maximal spatial vector
- Spatial magnitude of maximum rightward vector (MRSV)

Table II Correlation coefficients for the best individual correlations between VCG and hemodynamic measurements

Variable	*r*	*P*
RSVP		
X min	0 64	< 0 001
MRSV	0 59	< 0 001
Σ X	0 57	< 0 001
Y_{80}	−0 51	< 0 001
Max RA	0 49	< 0 001
QRS-rotation$_H$	0 49	< 0 001
ST vector	0 41	< 0 01
X_{70}	−0 38	< 0 01
Σ X−/Σ X+	0 37	< 0 01
Y_{60}	0 37	< 0 01
Qp/Qs		
ST Z	0 44	≈ 0 001
Z_{60}	−0 36	< 0 01
ST vector	0 32	< 0 05
QRS-duration	0 31	< 0 05
T Z	0 30	< 0 05
X_{80}	−0 29	< 0 05
X_{70}	−0 29	< 0 05
Z_{30}	0 28	< 0 05

Thirty patients had VCG recordings made within one week from the hemodynamic investigation, in the other 20 this interval ranged from four to 23 months (mean 10 months) In none of them was there any clinical or electrocardiographical progression during this period

For each patient 54 VCG measurements were derived (Table I) The emphasis was laid on a complete representation of information present in the QRS complex QRS rotation was coded as figure of eight when only a small part of the loop rotated opposite to the main direction Maximal rightward spatial vector (MRSV) was, according to previous experience[4] defined as the spatial magnitude of the maximal rightward vector and not as the maximal vector to the right of the midline Maximal anterior rightward deflection along the 135 degree axis was also recorded.[4] The sum of QRS forces oriented anteriorly and the corresponding sum of forces oriented to the right were derived from the areas below the deflections in the high speed scalar recordings The ratios of total anterior/posterior and right/left forces were also derived.

Hemodynamic data Right heart catheterization was made in all subjects and angiocardiography was made in all in whom there was a suspicion of additional defects Peak systolic right ventricular pressure recorded at rest (reference level anterior axillary line-fourth intercostal space), and the pulmonary to systemic flow ratio (Qp/Qs) calculated from the oxygen saturations (using the saturation in the superior vena cava as 'pre shunt value) were selected as the sole hemodynamic variables In addition, the casual systolic blood pressure was recorded as an index of stimulus to left ventricular hypertrophy

Data treatment The 54 VCG data systolic blood pressure age and sex were used as independent variables and RVSP and Qp/Qs were successively used as dependent variables in a multiple regression computer program (BIMD 09) The properties of this program have previously been outlined[4,7] At each step of computation the criterion for selecting a new variable is the F test As limiting F value for the entering and removal of variables 5 0 was chosen corresponding to a significance level of about 0 05 Through this process the optimal linear equation on the form

$$\text{RVSP or Qp/Qs} = a + b_1x_1 + b_2x_2 + \quad + b_nx_n$$

is computed

Results

Seventeen of the correlations between simple VCG data and RVSP were found to be significant at the five per cent level 10 were also significant to the one per cent level and six at the 0 1 per cent level (Table II) As seen the best individual predictor of pressure was found to be the simple

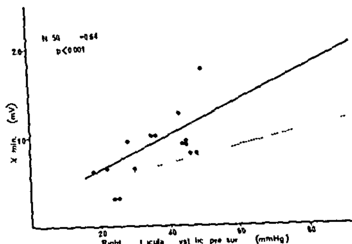


Fig 1 Relationship between maximum negative deflection in Lead X and RVSP Individual data and solid regression line represent subjects with atrial septal defects stippled line represents corresponding regression line for 38 patients with isolated pulmonary stenosis

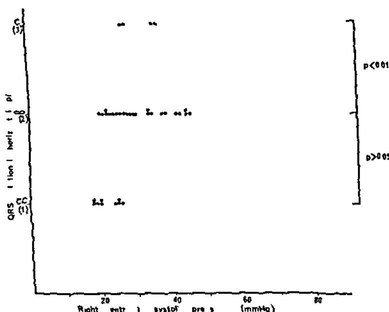


Fig 2. Relationship between direction of QRS rotation in horizontal plane and RVSP

maximal negative deflection in the X lead (Fig 1) This relationship was particularly reliable in its ability to exclude a high pressure when the X min was low The 95 per cent confidence interval of the correlation coefficient (0 64) is 0 78 to 0 44 thus the best predictor was not significantly better than the five following ones in Table II Nevertheless it is noteworthy that the simple X min measurement was superior both to the spatial voltage of the corresponding vector and to the total amount of forces oriented to the right The distribution of RVSP in the material may also be seen in Fig 1

As previously found for patients with pulmonary stenosis[4] a highly significant relationship was observed between RVSP and QRS loop rotation in the horizontal plane (Fig 2) However the relationship differed distinctly in the two conditions In atrial septal defects a much lower pressure was required to turn the loop rotation

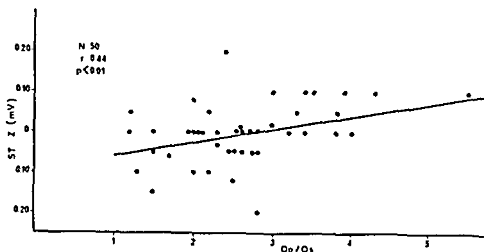


Fig 3 Relationship between ST deviation in Lead Z and Qp/Qs.

from counterclockwise to *figure of eight* and further to clockwise The clockwise loops on atrial septal defects were in general also more narrow than in pulmonary stenosis In pulmonary stenosis a clockwise oriented loop indicated a RVSP exceeding 100 mm Hg, whereas in atrial septal defects pure clockwise loops were seen down to 27 mm Hg Because of this increased sensitivity to pressure the horizontal plane loop rotation lost much of the diagnostic value found in pulmonary stenosis

This difference in RVSP VCG relationship was also observed when quantitative VCG variables in the two conditions were compared As an example the regression lines for the X min RVSP relationship are shown in Fig 1 For pulmonary stenosis the line is drawn from previously reported data on 38 patients (r=0 68) [4] As seen in atrial septal defects the regression line is dislocated up and to the left, indicating an increased VCG sensitivity to pressure in this condition The difference between the lines is statistically significant (for the slopes $p < 0.01$) Similar relationships were found for other quantitative variables

The degree of deviation from the pressure VCG regression line was not found to be useful for prediction of flow in the individual case This is also reflected in the observation that subjects falling above the line had only slightly higher flow ratios than those falling below

RVSP and Qp/Qs were found to be completely unrelated ($r = 0.02$) As expected the VCG correlations with flow were much poorer than with pressure but six correlations were significant at the five per cent level and two also at the one per cent level (Table II) The best individual correlation was found with the ST deviation in Lead Z (Fig 3) Patients taking digitalis were similarly distributed in Fig 3 as the others QRS duration was among the variables which correlated significantly with flow

The multiple regression computer program with RVSP as the dependent variable proceeded through six steps ending with a formula based on 4 VCG variables

RVSP =
$$6.3 + 9.2\,QRS\,rot._{H} + 28.5\,X\,min + 13.8\,X\,60 + 9.8\,Z\,min.$$

All the coefficients in this equation had standard errors of less than one third of their values. *By* means of this equation the correlation between predicted and measured RVSP increased to 0 80 with a 95 per cent confidence interval of 0 67 to 0 88 (Fig 4) Thus the results were probably significantly better than those obtained with the best individual variable ($p < 0.05$)

Multiple regression analysis with Qp/Qs as the dependent variable was unsuccessful since it did not proceed beyond the first step A computer run with flow as independent variable in pressure prediction was also unsuccessful since flow did not enter the equation

Discussion

Materials and methods The problems related to human interpretation of VCG data *the* general aspects of predicting hemodynamic data from VCG variables and the specific problems in the use of multiple regression analysis for this purpose have all been discussed previously [4,6] The present material differs from most previous ones dealing with the *ECG VCG* in atrial septal defects in the large age range of the patients and the lack of exclusion of patients with a QRS

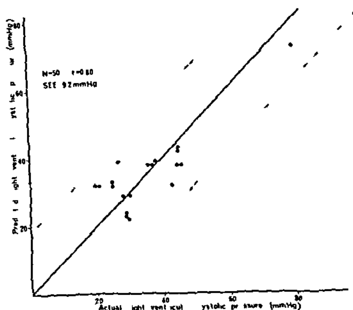


Fig 4 Relationship between measured and equation predicted RVSP The dotted lines delineate the ± 2 S E E area from the line of identity

duration above the commonly accepted bundle branch block limit Both these factors may have reduced the correlations but they have on the other hand, increased the applicability of the method. The time gap between the two investigations in several patients may also have deteriorated the results somewhat. The study is the first of its kind using the axial lead system

Individual VCG hemodynamic correlations Previous studies have in general found poorer relationships between electrical and hemodynamic data in atrial septal defects than in pulmonary stenosis Some have found no significant correlations whatsoever[1,3] while others have reported significant but practically little useful relationships[9,10]

Recently however Edmonds and associates[11] and Ellison and Restieaux[12,13] have reported useful correlations between RVSP and VCG data recorded with the Helm and Frank lead system The present report confirms these observations for the axial lead system and also confirms that RVSP is the fundamental hemodynamic factor which determines the ECG VCG pattern in atrial septal defects. The individual correlations found in this study were somewhat poorer than the best reported by Edmonds and associates[11] in 26 patients and by Ellison and Restieaux[12,13] in 40 patients The better results of Edmonds and associates may partly be explained from the larger pressure range in their material giving higher coefficients of correlations than in the other studies but similar standard errors of pressure estimate (S E E) The differences between the studies may otherwise be fully explained by differences in patient selection and chance and do not indicate a significant superiority of one lead system or method of analysis[14,15] The three studies all agree in that the most valuable data for pressure prediction is some expression of maximal forces oriented to the right However this study indicates that the MRSV is only one among several VCG variables which may be used to express these forces[4]

Right ventricular pressure and flow were found to be completely unrelated entities The VCG variables which correlated significantly with flow were also different from those which correlated with pressure Most of them indicated that the effect of an increased flow is to dislocate the terminal part of the QRS complex anteriorly and to the right and to dislocate the ST and T in a posterior direction However all the correlations were poor and should be interpreted with caution since the requirement for significance levels must be increased when so many variables are tested. Even the best predictor of flow (Fig 3) was poor and has hardly any practical value It is of theoretical interest, however that the QRS duration was found to be related to flow This gives

further support to the concept that the QRS widening in atrial septal defects usually is caused by the right ventricular dilatation as such and not by localized right bundle branch block [16]

Only a few significant flow ECG relationships have previously been reported. Edmonds and associates[11] found no significant correlations with flow until the subjects with pulmonary hypertension had been excluded. Ellison and Restieaux[12 13] did not test so many VCG data and found no positive relationships Walker and co workers,[10] however, noticed a relationship between flow and QRS duration

Three factors may serve to explain the poor correlations between VCG and flow First, flow loads are almost always associated with some degree of pressure loading Pressure seems to be a much stronger factor than flow for the induction of ventricular hypertrophy probably because pressure work induces a larger increase in myocardial oxygen demand.[17] Therefore any correlation between VCG and flow will tend to be hidden by the dominant influence of pressure Second, the reliability of flow measurements is much less than that of pressure measurements Therefore a good actual correlation between VCG and flow may be considerably reduced by the inaccuracies of both types of measurements involved [6] Third flow may be expected to exert its influence upon the ECG through its relation to right ventricular muscle mass and volume but this relation is probably rather complicated It is also possible that other means of expressing right ventricular flow than the ratio used would have yielded better results

As evidenced by the comparison with the VCG pressure relationships seen in pulmonary stenosis, however, the increased right ventricular volume in atrial septal defects nevertheless has a profound influence on the VCG Both qualitative (Fig 2) and quantitative (Fig 1) VCG data show that the increased volume sensitizes the right ventricle to the effect of pressure—electrocardiographically and probably also anatomically One interpretation is that an isolated flow load has only small ability to induce hypertrophy but, when a pressure load is added the hypertrophic stimulus from this becomes markedly augmented

The similarity of the type of VCG changes in the two types of defects as well as the predominant influence of pressure on the VCG picture also in atrial septal defects indicate that there is no fundamental difference between "systolic and "diastolic' overloading in electrocardiography [16] The important thing is not different ECG patterns but rather a similar type of relationship between pressure and ECG VCG, although on a different level With increasing pressure the VCG pattern passes through about the same stages but at different rates

Combining of VCG data The most important result of the present study is that a substantial and probably significant improvement of the correlations could be obtained by means of combined VCG data selected from a multiple regression analysis This approach is logical in a situation in which a large number of VCG variables are correlated with pressure and are also more or less intercorrelated [4] Apart from the initial selection of variables to be tested the approach is empirical and detached from a priori physiological theories In this manner the useful noninvasive technique of pressure prediction from VCG data may be improved [4] The equation presented should be regarded as one of the alternative methods of extracting the maximal information from the available VCG data and too much attention should not be paid to which variables are actually selected [4]

The practical application of selected regression equations, and in particular equations derived from multiple regression analysis on other samples, is dangerous [4] The equation ought to be tested on a secondary sample before it can be accepted as an improvement of practical value However the large number of patients compared with the low number of variables in the equation indicate that this in fact reflects general properties of the atrial septal defect population and not casual relationships

Edmonds and associates[11] appear to be the only workers who have applied multiple regression analysis to this problem They found no improvement of the VCG pressure correlations but some improvement of flow prediction Their poorer results from data combination may be explained by sample size and by different ways of selecting the variables for entering the computer program [4]

Both the individual correlations and the benefit from data combination were somewhat poorer in this material than in the study of pulmonary stenosis [4] The result is however

somewhat better in terms of standard error of pressure estimate.

Right heart catheterization is commonly performed in patients with atrial septal defects with three purposes (1) verifying the diagnosis, (2) excluding additional congenital defects and (3) diagnosing complications especially pulmonary hypertension The present work has relevance to the latter purpose and confirms that VCG is able to exclude pulmonary hypertension or pulmonary stenosis of importance with confidence especially when combined VCG data are used. Therefore if the diagnosis of atrial septal defect may be accurately made by clinical means, the need for complete preoperative right heart catheterizations may be reduced. It has recently been shown that VCG may also have a high ability to differentiate patients with atrial septal defects from normal subjects[19] Reliable noninvasive indicator methods are now available for estimating shunt presence and size If such a method is combined with a VCG estimate of RVSP the result may be so reliable that routine catheterization can be omitted in selected patients. Before heart catheterization can be routinely omitted, precise clinical methods for discrimination between atrial septal defects and other types of congenital heart disease must also be available The greatest field of application for the method will however be in patients who have previously been investigated hemodynamically and in whom signs of improvement or deterioration of RVSP are sought

Summary

A search for simple and combined VCG data which could optimally predict right ventricular systolic pressure (RVSP) or shunt size was made in 50 patients with atrial septal defects of the secundum type VCG was recorded by means of the axial lead system and a multiple regression computer program was applied. Fifty four VCG data, age sex, and systolic blood pressure were tested as independent predictors

Seventeen VCG data were significantly correlated with RVSP and six with flow The best individual variable was the simple maximal negative deflection in Lead X ($r = 0.64$ $p < 0.001$) The correlations with flow were poorer but of theoretical interest. Distinctive differences in the VCG RVSP relationships were found in atrial septal defects compared with those in pulmonary stenosis indicating that the increased flow sensitizes the right ventricle to the effect of pressure

Through multiple regression analysis an equation based on four vectorcardiographic variables was derived This equation improved the RVSP VCG correlations significantly ($p < 0.05$ $r = 0.80$) The study confirms that vectorcardiogram is a reasonably reliable method for estimating RVSP in patients with atrial septal defects and that the use of combined VCG data may improve the method considerably

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Vectorcardiographic changes following coronary artery bypass surgery

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Numerous studies have documented that coronary artery bypass surgery significantly alleviates angina pectoris in the majority of patients [1-5] This is thought to relate to increasing myocardial blood flow to ischemic myocardium distal to proximal occlusive disease

The incidence of operative myocardial infarction has been reported to be between 3 and 29 7 per cent [6-11] Several of these studies include patients undergoing Vineberg operations in conjunction with bypass as an additional revascularization procedure

The postoperative incidence of pericarditis has limited to QRS changes alone the electrocardiographic criteria for myocardial infarction Similarly the vectorcardiogram (VCG) would be limited to interpretation of the QRS loop alone To our knowledge the affect of open heart surgery itself on the QRS loop of the VCG is unknown We have compared the pre and postoperative VCG of patients undergoing saphenous vein bypass grafts to a group of control patients having open heart surgery for other reasons in an attempt to further clarify the true incidence of myocardial infarction following coronary artery bypass surgery

Materials and methods

Eighty five patients (Table I) underwent coronary artery bypass surgery (CABS) at Walter Reed General Hospital from November 1970 to December 1972 The group included 71 men and 14 women Their ages ranged from 23 to 63 years (average age 47 years) The indication for surgery in each was severe angina pectoris not controlled by medical therapy Seventy four per cent (63/85) had previously suffered at least one myocardial infarction Clinical congestive heart failure was evident in 16/85 (18 8 per cent) Eighteen of 85 (21 per cent) had one graft, 40/85 (47 per cent) had two grafts and 27/85 (32 per cent) had three grafts In addition 13/85 (15 3 per cent) had left ventricular aneurysmectomy The surgical mortality rate was 10/85 (11 8 per cent)

Of the above group the last 34 consecutive patients were evaluated by pre and postoperative vectorcardiograms (VCG s) and form the basis for this study These patients are representative of the entire group

Preoperatively each patient was evaluated by right and left heart catheterization with coronary and left ventricular angiography Coronary occlusive disease was considered significant if the luminal diameter was diminished by more than 50 per cent. Using this criterion 2/34 (6 per cent) had single vessel, 12/34 (35 per cent) had double vessel and 20/34 (59 per cent) had triple vessel disease Resting LVEDP was elevated greater than 12 mm. Hg in 5/34 (14 5 per cent)

In addition to a standard 12 lead electrocardiogram (ECG) each patient had a pre and postoperative VCG Each VCG was recorded in three planes using the Frank lead system with electrode placement in the fifth intercostal space The VCG s were recorded on an Electronics for Medicine light beam oscilloscopic photographic recorder using a VCG channel The VCG loops were interrupted at 2 msec intervals and the fre

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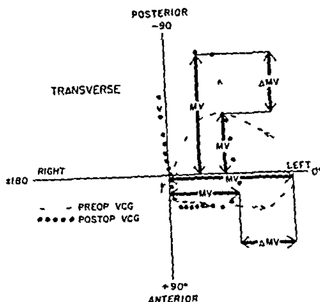


Fig 3. The pre- and postoperative transverse loops are depicted. The maximal left and posterior voltages are determined. The voltage change (Δ) between the vectors is determined

control mean for that point. For a change to be considered significant it was required that an angle must change more than the mean change of the control plus 2 standard deviations in either direction from the corresponding angle on the preoperative VCG (Fig 2) The magnitude of change at each point which must be exceeded to be considered significant is summarized in Table II

In addition the maximal voltage in four directions for each plane was measured in the pre and postoperative VCG of the controls (Fig 3) The mean change for each value was determined. Voltage changes in the CABS patients were then compared to the control mean plus 2 standard deviations The magnitude of change necessary to be considered significant is depicted in Table III

A postoperative VCG in a CABS patient was considered to have significantly changed, more than could be accounted for by surgical intervention itself if at least two consecutive angles in the same plane or one voltage change in any plane was noted.

The ECG diagnosis of definite myocardial infarction was based on conventional criteria for QRS changes[12] The VCG diagnosis of definite myocardial infarction was based on criteria published by Chou and Helm[13]

Results

Excluding the 6 intraoperative deaths 79 patients were evaluated with pre and postoperative ECG s Utilizing accepted QRS criteria only the incidence of infarction of our entire group is 19/79 (24 per cent) Additional ECG changes include significant axis change (4 cases) loss of preoperative Q waves (1 case) and loss of R wave progression (3 cases)

Based on the VCG changes determined from our control group our subgroup of 34 VCG analyzed patients were divided into three groups (Table IV) There was no significant difference in the extent of preoperative disease or the number of vessels grafted among the three groups

Group I—Patients with classic QRS changes of myocardial infarction (12/34) or 34 per cent

Group II—Patients who significantly changed their postoperative VCG but who did not meet criteria for classic infarction These patients were subdivided into (A) Those with 2 consecutive angle changes with or without coexisting voltage change = 9/34 (26 4 per cent) and (B) Those with voltage change only 4/34 (11 8 per cent)

Group III—Patients who did not significantly change their postoperative VCG = 9/34 (26 4 per cent)

Group I Twelve of 34 patients demonstrated

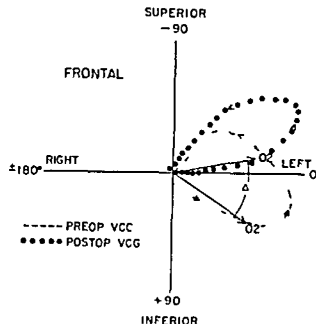


Fig 1 The pre and postoperative frontal plane loops are depicted The 20 msec vector of each loop is marked and angle of its vector from null determined The change in angle (Δ) of each 10 msec vector in all planes was determined as shown.

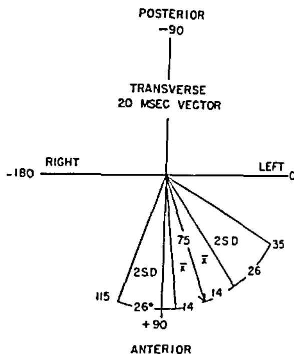


Fig 2 This depicts the magnitude of change in either direction that an angle must change to be significant The mean change for the 20 msec vector of the transverse plane plus 2 standard deviations are shown The postoperative analogous angle must exceed these limits to be significant

Table I Coronary artery bypass surgery at Walter Reed General Hospital—85 patients

Previous M I	63/85 (74%)
Clinical CHF	16/85 (18 8%)
Grafts inserted	
Single	18/85 (21%)
Double	40/85 (47%)
Triple	27/85 (32%)
L V aneurysmectomy	13/85 (15 3%)
Mortality rate	10/85 (11 8%)

Abbreviations M I = myocardial infarction CHF = congestive heart failure LV = left ventricle

Table II Angle changes in degrees

Second	*Frontal*	*Transverse*	*Sagittal*
01	51	28	42
02	22	40	45
03	52	61	64
04	79	60	38
05	92	56	32
06	30	72	41

quency response was 25 Hz VCG s were obtained no earlier than one week preoperatively In each case the VCG was recorded by the same individual both pre and postoperatively to decrease the chance of electrode placement variability ECG's were obtained one day preoperatively and at varying intervals during the postoperative period

In addition 15 patients undergoing cardiac surgery other than CABS had pre and postoperative VCG's and served as controls Procedures on these patients included (1) aortic valve replacement in four, (2) mitral valve commissurotomy in six, (3) mitral valve replacement in one (4) atrial septal defect repair in three and (5) repair SVC to LA shunt in one

Changes in the postoperative VCG of these patients were used as controls to minimize the chance that open heart surgery itself was responsible for changes in the postoperative VCG of CABS patients

To analyze the control VCG's the angle of each 10 msec vector from the null point was determined for both the pre and postoperative VCG s The change in angle at each 10 msec vector was determined between the pre and postoperative VCG (Fig 1) The mean change at each 10 msec vector in each plane was determined for all the controls

The pre and postoperative VCG s of the CABS patients were similarly analyzed The angle changes at each 10 msec were compared to the

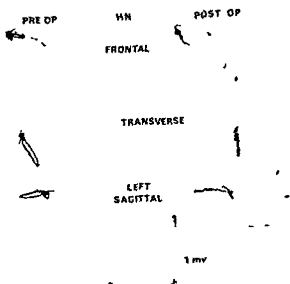


Fig 5 Patient H N The 10 20 and 50 msec vectors in the frontal plane have changed, directing the initial forces superiorly and clockwise suggesting changes in inferior depolarization There has also been posterior rotation and diminution of leftward forces most marked in the transverse plane

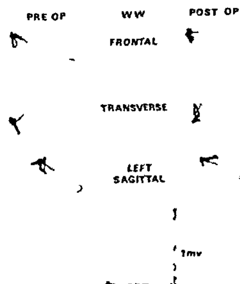


Fig 6 Patient W W There is no significant change in angle However the entire loop has diminished in amplitude being most marked and significant in the leftward forces

correlation with graft occlusion Similarly in restudy of our Group I patients three of four patients were noted to have all grafts patent. In addition restudy in six of 13 patients in Group II having a total of 14 grafts has shown all but one graft to be patent. This would indicate that early graft closure is not the only cause of myocardial infarction following saphenous vein bypass surgery

The incidence of intraoperative myocardial infarction may have been previously underestimated.[14,16] Analysis of ST segment and T wave changes following thoracotomy is hazardous because of localized and generalized pericarditis Therefore only QRS criteria for myocardial infarction are accepted as valid evidence of myocardial infarction It has been suggested that if more sensitive methods of detection were available the recognition of myocardial damage would increase

Pre and postoperative VCG s were performed on the control patients to analyze the effect of thoracotomy pericardiotomy cardiopulmonary bypass and insertion of a left ventricular sump on the postoperative VCG Changes noted in the postoperative VCG of a saphenous vein graft bypass patient which exceeded the limits of change determined by the controls were believed not to be related to open heart surgery itself

Thirty eight per cent of our patients (Group II) although not meeting VCG criteria for myocardial infarction significantly changed their QRS loop on the postoperative VCG We believe that changes seen in these Group II patients are related to alteration in conduction or loss of myocardium which are either too small or distributed in a manner such that they are not recognized by classic criteria as myocardial infarctions. Six of nine patients altered their 10 and 20 msec vectors the portion of the loop seen to vary most frequently in classic myocardial infarction The remaining three patients altered their 30 to 50 msec vector in the transverse or sagittal planes resulting in significant anterior or posterior shifts of the QRS loop Such redistribution of myocardial forces suggests anterior or posterior wall damage

The high incidence of graft patency in Groups I and II would imply that intraoperative manipulation sufficiently compromises myocardial circulation to cause myocardial damage regardless of the ultimate fate or the graft. The degree and/or location of the intraoperative damage would determine the extent of alteration noted on the postoperative VCG This can range from classic myocardial infarction to more subtle changes in conduction or redistribution of myocardial forces The lowest graft patency rate

Table III Voltage changes in millivolts

	Frontal	*Transverse*	*Sagittal*
Superior	18	—	18
Inferior	42	—	42
Anterior	—	15	15
Posterior	—	61	61
Right	26	26	—
Left	28	28	—

Table IV VCG subgroup—34 patients

Group	I = Definite M I	12/34 (35 4%)
Group	II = VCG changes not diagnostic of M I	
	A = Angle and/or voltage changes	9/34 (26 4%)
	B = Voltage changes only	4/34 (11 8%)
Group	III = No VCG change	9/34 (26 4%)

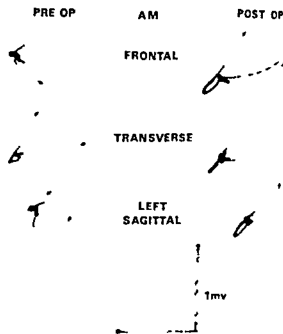


Fig 4 Patient A M The 10 to 30 msec vectors of the frontal and sagittal planes are significantly changed This shifts the axis superiorly however criteria for left anterior hemiblock are not met There is significant change in superior and inferior distribution of forces.

classic VCG changes of myocardial infarction The infarct was identified by ECG in 11 patients. The twelfth patient had an anterolateral infarct by VCG which would not be identified by ECG There were eight inferior, three anterolateral, and one anteroseptal wall myocardial infarctions In each instance the area of infarction corresponded to the location of graft placement

Group II Nine of 34 patients whose postoperative VCG did not demonstrate infarction were noted to have at least two consecutive angles within the same plane which exceeded the control values This observation was also noted in all patients whose VCG met accepted criteria for myocardial infarction The VCG s seen in Figs 4 and 5 demonstrate definite changes representative of Group II (A) patients

The noted changes correlated with an area of graft insertion, however six of nine of these patients had three grafts making anatomic correlation difficult.

Four of 34 patients had only voltage changes which were greater than would be expected from the control group The VCG seen in Fig 6 shows a representative patient from Group II (B)

Group III Nine of 34 patients including two having left ventricular aneurysmectomy, exhibited no change in their postoperative VCG or ECG These patients did not differ from those in the previous two groups in extent of coronary artery disease or in the degree of left ventricular dysfunction

Four patients in Group I and six patients in Group II have been restudied Nineteen of 22 grafts (86 5 per cent) remain patent Both grafts in a single Group I patient and one of three grafts in a single Group II patient were occluded. In contrast, only 8/13 (61 5 per cent) grafts remain patent in Group III patients who did not change their postoperative VCG

Discussion

At Walter Reed Army Medical Center the over all incidence of classic QRS changes of myocardial infarction on electrocardiogram following saphenous vein bypass surgery is 19/74 (24 per cent) Previous studies have demonstrated that surgical mortality rate and subsequent graft patency are related to the degree of disease and preoperative left ventricular function [14] Similarly we believe the incidence of myocardial infarction in our series reflects the severity of preoperative disease

Manly and Johnson[14] noted a 5 per cent incidence of myocardial infarction following saphenous vein bypass and related it to early graft closure In patients who suffered an acute myocardial infarction at surgery and subsequently died Brewer and colleagues[15] noted no

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8/13 (16 5 per cent) occurred in patients who did not change their postoperative VCG, giving further support to the thesis that early graft closure is not the only cause of operative myocardial infarction

In our series the occurrence of intraoperative myocardial infarction has been related to two angiographic findings The area of infarct is supplied by a vessel which either receives no collaterals or whose collaterals are supplied from a diseased major vessel Twelve of 14 patients with either no collateral or collaterals supplied by a diseased vessel which was grafted first had classic QRS changes of myocardial infarction Conversely none (0) of seven patients whose collaterals arose from a nondiseased major coronary vessel had evidence of myocardial infarction The difference is statistically significant by Chi square test with Yates Correction at a $p < 0.01$ *Having made this observation, we are presently* trying to determine whether alteration of the surgical order of graft insertion might affect the incidence of myocardial infarction during bypass surgery

The comparison of pre and postoperative VCG s in the manner described is a sensitive method of detecting intraoperative alterations of myocardial depolarization Perhaps this method of analyzing VCG's in conjunction with other techniques such as iso enzymes of CPK will bring to light the true incidence of myocardial infarction associated with saphenous vein bypass surgery

Summary

Myocardial infarction (MI) has been reported to occur in about 15 per cent of patients following coronary artery bypass (CAB) surgery Preoperative and postoperative electrocardiograms (ECG) were evaluated in 85 patients Thirty four of these patients also had pre and postoperative vectorcardiograms (VCG) Fifteen additional patients undergoing open heart surgery were used as controls These included aortic valve replacement (in 4), mitral valve commissurotomy (in 6) mitral valve replacement (in 1) atrial septal defect repair (in 3), and repair SVC to LA shunt (in 1) Pre and postoperative VCG's were analyzed in three planes The angle of each 10 msec vector was measured The maximal voltage was determined along each axis in each plane Mean changes in these parameters were determined for the controls Change exceeding two standard deviations from the control mean was considered *abnormal and not explainable* by trauma of open heart surgery itself Excluding the six intraoperative deaths, 19/79 (24 per cent) had QRS changes of myocardial infarction by ECG Changes were considered significant in the postoperative VCG if they occurred in at least two consecutive angles in one plane or in the maximum voltage in one axis The postoperative VCG depicted MI in 34 per cent (12/34) In the absence of classic criteria for MI a significant change in VCG angle occurred in 26 4 per cent (9/34) The voltage in at least one axis changed *significantly in 11 8 per cent (4/34)* A change in the postoperative VCG was demonstrated in 73 5 per cent (25/34) The pre and postoperative VCG is a sensitive method of detecting subtle changes *in conduction or loss of myocardium seen in the* majority of patients following CAB surgery

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Table I Uncorrected values for systolic time intervals in patients with AMI

Patient	Resting (msec)				After tachycardia (msec)			
	QS_2	LVET	PEP	HR (beats/min.)	QS_2	LVET	PEP	HR (beats/min.)
1	347	264	83	80	335	244	91	95
2	264	175	89	112	263	157	103	100
3	344	231	111	83	327	213	113	95
4	375	268	107	64	364	243	121	86
5	347	224	121	71	329	206	123	92
6	397	267	129	61	335	205	130	100
7	357	278	79	78	355	273	82	81
8	384	268	116	73	374	227	152	100
9	345	221	124	81	320	209	111	95
10	324	219	106	89	323	231	93	86
11	349	260	90	59	348	251	98	66
12	397	290	102	71	384	292	92	75
13	350	228	110	85	327	213	113	95

Table II Uncorrected values for systolic time intervals in controls

Control subject	Resting (msec)				After tachycardia (msec)			
	QS_2	LVET	PEP	HR (beats/min.)	QS_2	LVET	PEP	HR (beats/min.)
1	416	311	105	61	390	284	107	77
2	438	325	113	65	370	289	81	77
3	390	299	91	63	372	288	84	85
4	398	313	85	66	388	298	90	70
5	419	302	117	66	395	295	100	84
6	380	302	78	64	362	286	76	83
7	404	315	89	67	387	305	82	81
8	396	321	75	55	372	288	84	90
9	360	280	79	68	334	259	75	94

per cent above resting levels to an average heart rate of 110 for ten minutes (range 100 to 120 per minute). In two patients atrial pacing was initiated at a rate of 110 for ten minutes and then stopped. In all subjects the heart rates were allowed to recover for 20 minutes before systolic time intervals were again re-measured.

The QS_2 interval was measured from the onset of the Q wave to the first high frequency aortic component of the second heart sound. The left ventricular ejection time (LVET) was measured from the onset of the rapid rise of the carotid pulse to the incisura. The pre-ejection period (PEP) was derived by subtracting the LVET from the QS_2. The values for QS_2, PEP, and LVET were *corrected* for heart rate according to the regression formula of Weissler and associates.[4]

QS_2 (corrected) in msec $= QS_2 + 2.1 \times HR$ (men)

$= QS_2 + 2.0 \times HR$ (women)

LVET (corrected) in msec $= LVET + 1.7 \times HR$ (men)

$= LVET + 1.6 \times HR$ (women)

PEP (corrected) in msec $= PEP + 0.4 \times HR$ (men and women)

The PEP/LVET ratio was obtained by dividing the *uncorrected* pre-ejection period by the *uncorrected* left ventricular ejection time.

The effect of sinus tachycardia on the phases of left ventricular systole during acute myocardial infarction in man

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Washington D C

Persistent sinus tachycardia following myocardial infarction usually occurs as a manifestation of heart failure and is associated with a prognosis more serious than that of transient ventricular tachycardia[1] While this increase in heart rate may have a beneficial effect on the whole body by maintaining critical blood flow to vital organs the increase in cardiac work produced by the tachycardia places an undesirable stress on an already ischemic myocardium It is well recognized that heart rate is one of the determinants of myocardial oxygen consumption[2] In fact the detection of latent ischemic heart disease by intentionally producing electrocardiographic (ECG) evidence of myocardial ischemia with atrial pacing is based on that principle[3] On the other hand increases in the heart rate induced by atropine or atrial pacing to 90 or 100 per minute have been very succesful in the treatment of life threatening bradyarrhythmias immediately following myocardial infarction In order to determine the effect of brief periods of tachycardia on myocardial function systolic time intervals were measured before and after a brief period of tachycardia induced either by intravenous atropine or by atrial pacing in patients with uncomplicated myocardial infarction A series of normal subjects served as controls

Materials and methods

Patients seen in the Georgetown University Hospital coronary care unit (CCU) with an admitting diagnosis of acute myocardial infarction (AMI) were screened Patients selected for study were only those with *uncomplicated* AMI presenting with a typical history of chest pain, whose ECG demonstrated diagnostic evolutionary changes with Q wave formation and whose enzymes showed characteristic elevations Patients were eliminated from the study if they had bundle branch block, clinical or radiologic evidence of congestive heart failure, systemic hypertension valvular heart disease, or if they were receiving a digitalis preparation Thirteen patients were found to meet the criteria for selection There were eight men and five women ranging in age from 42 to 65 years, with a mean age of 56 years Seven patients had inferior wall myocardial infarction and six had anterior wall myocardial infarction All were in normal sinus rhythm Eight male and one female healthy control subjects without evidence of heart disease were selected for comparison They ranged in age from 24 to 49 years, with a mean age of 29 years.

Systolic time intervals were measured between 8 A M and 12 noon with the subject in the fasting state The phonocardiogram carotid pulse and an ECG lead selected for the earliest Q wave were recorded on an Electronics for Medicine DR 8 Recorder at a paper speed of 150 mm per second Heart sounds were recorded during quiet respiration in the supine position with the microphone placed in the second left intercostal space The carotid pulse was obtained by a funnel pick up connected by a short rubber tubing to a Statham P23Db pressure transducer The systolic time intervals were first measured in the resting state Then in 11 patients and nine control subjects intravenous atropine was given sufficient to raise the heart rate approximately 50

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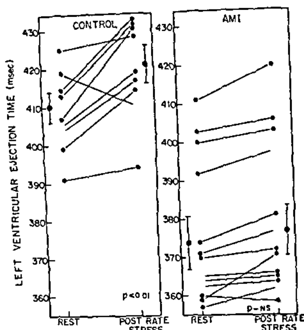


Fig 3 The left ventricular ejection time corrected for heart rate before and after rate stress Bar = mean ± S E.M

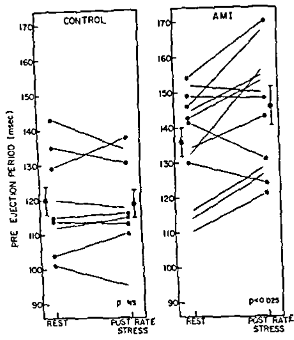


Fig 4 The pre ejection period corrected for heart rate before and after rate stress Bar = mean ± S E.M

pared to the resting state ($p < 0.025$) In the MI group in nine of the 13 subjects the duration of PEP increased in two it remained unchanged and in two it decreased (Table III)

PEP/LVET ratio The PEP/LVET ratio was significantly different in the control group (0 30 ± 0 05) when compared to the myocardial infarction group (0 43 ± 0 09) [$p < 0.02$] (Fig 5) After rate stress the PEP/LVET ratio in control subjects remained unchanged (0 29 ± 0 05) However following rate stress the PEP/LVET ratio lengthened in nine of 13 patients in the infarction group This increase of the PEP/LVET ratio was significant when compared to resting values (0 49 ± 0 13) [$p < 0.05$] (Fig 5) (Table III)

Although mean values for systolic time intervals were significantly different after tachycardia individual values for controls and patients with myocardial infarction were not sufficiently different to allow discrimination of individual patients from normal subjects One exception to this was the PEP/ET ratio After tachycardia the PEP/ET ratio was greater than 0 36 in nine of 11 patients but in none of the controls (Fig 5) (Table III)

No adverse effects were seen clinically from induced tachycardia Neither clinical heart failure hypotension nor arrhythmia was seen in the subsequent period All patients survived and were discharged from the CCU

Discussion

Our patients with acute transmural myocardial infarction had a diminished QS_2 and LVET but a prolonged PEP during the resting state These results are similar to those reported by others during acute myocardial infarction in man[5,6] and in dogs[7] However when the patient was stressed with a tachycardia and then allowed to return to a slower heart rate the QS_2 became prolonged This was predominantly a result of prolongation of the PEP without significant change in LVET Thus the PEP/LVET ratio increased In normal subjects the QS_2 also prolonged after the stress of tachycardia but primarily because of prolongation of the LVET with no change in the PEP so that the PEP/LVET ratio remained relatively unchanged

Prolongation of the PEP has been reported in heart failure and in AMI[5,6,8] Factors which may prolong the PEP are (1) an increase in ventricular depolarization time (2) high aortic diastolic pressure and (3) a decrease in the rate of left ventricular pressure development during the isovolumetric period (isovolumetric dp/dt)[8] In our patients there was no evidence of prolonged

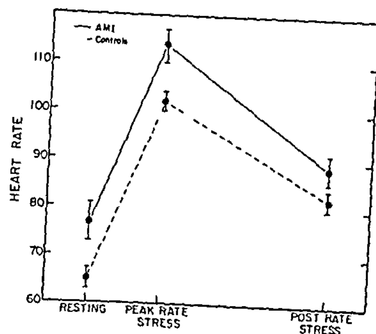


Fig 1 Mean heart rate in beats per minute with standard error of the mean (S E M) in control and acute myocardial infarction group at rest at peak heart rate and after return toward the resting rate

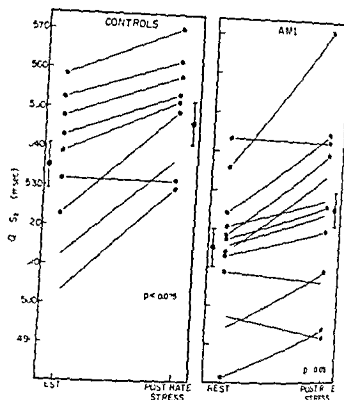


Fig 2 The Q S_2 interval corrected for heart rate before and after rate stress Bar = mean ± S E M

Results

The uncorrected values obtained from measurement of systolic time intervals in all subjects are contained in Table I and II

Heart rate At rest the mean heart rate in the control group was 64 per minute ± 4* and 77 per minute ± 14 in the infarction group (Fig 1) During the rate stress there was at least a 45 per cent increase in the heart rate in both groups The peak rate during rate stress in the control group averaged 102 ± 5 and in the infarction group averaged 112 ± 7 The average dose of atropine needed to induce this tachycardia in the control group was 1 7 mg (range 1 2 to 2 0 mg) and in the infarction group was 1 3 mg (range 0 8 to 1 8 mg) After rate stress the heart rates returned toward the normal range 82 per minute ± 7 in the control group and 88 per minute ± 11 in the infarction group (Fig 1 Table III)

Electromechanical systole In the resting state the duration of total electromechanical systole the Q S_2 interval was 535 msec ± 19 in the controls and 515 msec ± 18 in the myocardial infarction group These are significantly different ($p < 0.025$) (Fig 2) After rate stress the Q S_2 lengthened in the control group (547 msec ± 14 [$p < 0.025$]) and in the myocardial infarction group (525 msec ± 28 [$p < 0.05$]) This increase was of equal magnitude in both groups (Table III)

Left ventricular ejection time At rest the LVET in the control group was considerably longer than the myocardial infarction group (410 msec ± 12 for controls 371 msec ± 21 for AMI) (Fig 3) The difference between these groups was significant ($p < 0.001$) In three patients with myocardial infarction the resting LVET was normal After rate stress an increase in LVET was seen in all but one subject in the control group The mean value was 421 msec ± 13 ($p < 0.01$) However, in the myocardial infarction group the LVET remained essentially unchanged in seven patients slightly increased in six and diminished in one The mean LVET in the infarction group after induced tachycardia was 377 msec ± 25 and was not significantly different from resting values (p = NS) (Table III)

The pre ejection period At rest the pre ejection period averaged 120 msec ± 14 in the control group and 136 msec ± 15 in the myocardial infarction group ($p < 0.02$) (Fig 4) Following rate stress in the control subjects the PEP remained unchanged (119 msec ± 13) but lengthened in the myocardial infarction group (146 msec ± 20) This prolongation was significant when com-

* Values given are mean ± standard deviation

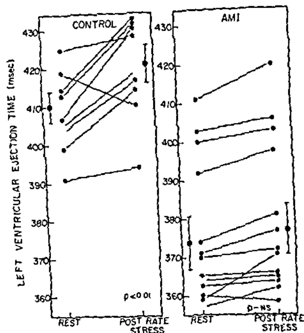


Fig 3 The left ventricular ejection time corrected for heart rate before and after rate stress Bar = mean ± S E M

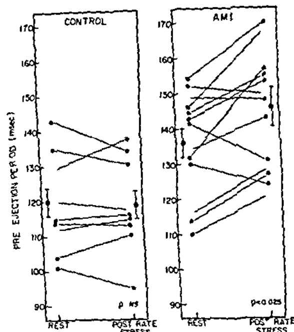


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Table III Systolic time intervals in controls and AMI patients before and after rate stress

	Control group (M ± S.E.M.)			AMI group (M ± S.E.M.)		
	Before rate stress	After rate stress	p value	Before rate stress	After rate stress	p value
Heart rate (beats/min)	64 ± 4	82 ± 7		77 ± 14	88 ± 11	
Q S2 interval (corrected in msec)	535 ± 19	547 ± 14	<0 025	515 ± 18	525 ± 28	<0 05
LVET (corrected in msec)	410 ± 12	421 ± 13	<0 01	374 ± 21	377 ± 25	N.S
PEP (corrected in msec)	120 ± 14	119 ± 13	N.S	136 ± 15	146 ± 20	<0 025
PEP/LVET ratio	0 30 ± 0 05	0 29 ± 0 05	N.S	0 43 ± 0 09	0 49 ± 0 13	<0 05

N S not significant.

ventricular depolarization time or elevated aortic diastolic pressure after induced tachycardia In creasing the heart rate by either atrial pacing or atropine over wide ranges of heart rates has been shown to have no effect on the PEP in normals [9] Weissler and associates[8] have suggested that the prolongation of PEP in heart failure is due to a diminished left ventricular dp/dt and Forrester and colleagues[10] have demonstrated a reduction of left ventricular dp/dt following AMI It seems likely then that the further prolongation of PEP in our nine cases after tachycardia was due to a further diminution in left ventricular dp/dt In two patients with myocardial infarction the PEP remained unchanged and in two others it shor tened One might postulate that in these patients the size of the infarct was sufficiently small to allow their ventricles to respond to tachycardia similarly to those of the controls The effect of enhanced catecholamine excretion which is known to occur during myocardial infarction might also explain the shortening of the PEP which occurred in two patients [8]

Previous studies have shown that the Q S_2 in terval[11] and the LVET[12] are shortened following AMI The shortened LVET can be caused by (1) a decrease in myocardial contractility (2) a decrease in stroke volume (3) digitalis or other inotropic drugs [13] (4) alteration in serum calcium levels [14] or (5) mildly elevated arterial pressure [15] It is known that stroke volume varies directly with left ventricular ejection time if aortic pressure and heart rate remain constant[15,16] and that stroke volume is diminished in acute myocardial infarction [17,18] In this study arterial pressure or digitalis state did not vary following rate stress Changes in serum calcium levels have not been reported following tachycardia Thus failure of the LVET to lengthen in our infarct group might well reflect the inability of stroke volume to increase after tachycardia

Six patients in the infarction group increased their LVET similarly to the controls. In four of these six patients the PEP also varied as in nor mal subjects This could be explained if the size of the infarct were so small that the effect of sinus tachycardia would be an increase in left ventricular stroke volume or myocardial contrac tility as in normal subjects However until estimation of infarct size can be accurately measured clinically this can be only speculated.

The patients in this series with myocardial in farction had elevated PEP/LVET ratios at rest, which increased further after recovery from tachycardia This increase in the PEP/LVET ratio may reflect a diminution in the ejection fraction of the left ventricle following tachy cardia [19]

There is evidence that tachycardia itself may have an adverse effect on the myocardium at the time of AMI Maroko and associates[21] have shown in dogs that sinus tachycardia induced during occlusion of a major coronary artery aug mented the ST elevation in the border of the ischemia area Redwood and colleagues[22] have shown that after occlusion of a coronary vessel in dogs the magnitude of the ST T elevations in the area of infarction is proportional to the heart rate

Kent and associates[23] have recently demon

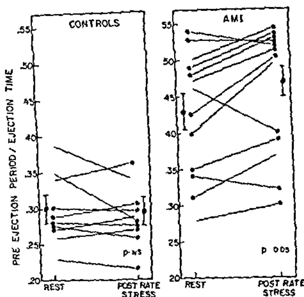


Fig 5 The ratio of the pre ejection period to the ejection time uncorrected for heart rate before and after rate stress. Bar = mean ± SEM

strated that tachycardia occurring during acute ischemic states reduces the electrical stability of the myocardium and lowers ventricular fibrillation threshold. In our patients with myocardial infarction the systolic time intervals indicated a decreased myocardial performance in the period after tachycardia. Perhaps sinus tachycardia and heart failure in myocardial infarction produce a self perpetuating cycle which contributes to the high mortality rate of this arrhythmia in myocardial infarction. Consequently we do not recommend routinely the induction of sinus tachycardia in the evaluation or treatment of patients with acute myocardial infarction.

Summary

The effect of a brief interval of sinus tachycardia on cardiac function was assessed in 13 patients with acute myocardial infarction and in nine control subjects. Systolic time intervals were used as indices of myocardial function. Intravenous atropine was given to 11 of the patients with AMI and to all the controls. Two patients with AMI had atrial pacing at a rate of 110 per minute for ten minutes. The systolic time intervals were measured in the resting control state and then again after the rate had returned toward the control heart rate after tachycardia. Patients with AMI had significant prolongation of electrical mechanical systole (the QS_2 interval) which was due to an increase in the pre ejection period. The left ventricular ejection time remained unchanged. Normal subjects also had a prolongation of the QS_2 interval but this was due to an increase in the ejection time not the pre ejection period. It would appear that transient increases in heart rate induced after AMI reduce myocardial performance in the subsequent period.

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Table III Systolic time intervals in controls and AMI patients before and after rate stress

	Control group (M I.S E.M)			AMI group (M I. S.E.M)		
	Before rate stress	After rate stress	p value	Before rate stress	After rate stress	p value
Heart rate (beats/min.)	64 ± 4	82 ± 7		77 ± 14	88 ± 11	
Q S2 interval (corrected in msec)	535 ± 19	547 ± 14	<0 025	515 ± 18	525 ± 28	<0 05
LVET (corrected in msec)	410 ± 12	421 ± 13	<0 01	374 ± 21	377 ± 25	N.S*
PEP (corrected in msec)	120 ± 14	119 ± 13	N.S	136 ± 15	146 ± 20	<0 025
PEP/LVET ratio	0 30 ± 0 05	0 29 ± 0 05	N.S *	0 43 ± 0 09	0 49 ± 0 13	<0 05

N S not significant.

ventricular depolarization time or elevated aortic diastolic pressure after induced tachycardia In creasing the heart rate by either atrial pacing or atropine over wide ranges of heart rates has been shown to have no effect on the PEP in normals [9] Weissler and associates[8] have suggested that the prolongation of PEP in heart failure is due to a diminished left ventricular dp/dt and Forrester and colleagues[10] have demonstrated a reduction of left ventricular dp/dt following AMI It seems likely then that the further prolongation of PEP in our nine cases after tachycardia was due to a further diminution in left ventricular dp/dt In two patients with myocardial infarction the PEP remained unchanged and in two others it shor tened One might postulate that in these patients the size of the infarct was sufficiently small to allow their ventricles to respond to tachycardia similarly to those of the controls The effect of enhanced catecholamine excretion which is known to occur during myocardial infarction might also explain the shortening of the PEP which occurred in two patients [8]

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Ventricular septal defect associated with aortic insufficiency Medical and surgical management

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Rochester N Y

The development of aortic insufficiency (AI complicating an often otherwise hemodynamically insignificant ventricular septal defect (VSD) is a well recognized problem of diagnosis and medical management The timing and type of surgical treatment are debatable This article presents our experience with seven patients in whom VSD repair was followed by either disappearance of AI or a significant decrease in the abnormal hemodynamics This is followed by a plan for the medical management of this condition and the selection of patients and timing for surgical repair

Clinical material

Seven male patients with AI associated with VSD underwent repair of the VSD without corrective surgery on the aortic valve (Patients who had aortic valve repair along with VSD closure were excluded from this study) All seven patients had right heart catheterization and six had aortic root biplane angiocardiography The patients were divided into two groups according to aortic root angiocardiographic findings (Fig 1) and additional information gained from operative findings In Group I were four patients with supracristal VSD and in Group II were three patients with infracristal VSD The preoperative findings are summarized in Table I

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Surgical management and results

All seven patients underwent VSD closure with the use of cardiopulmonary bypass The location of the VSD and the status of the aortic valve were inspected through a right ventriculotomy The VSD was closed by either direct suture or Dacron patch nothing was done to the aortic valve The operative findings and surgical procedures are summarized in Table II

In Group I the aortic insufficiency murmur disappeared two to three years after VSD closure except in Patient 4 in whom the VSD reopened soon after operation and the intensity of whose AI murmur remained unchanged In the three whose AI murmur disappeared after VSD closure no residual cardiac abnormality remained Phonocardiography revealed no diastolic murmur The findings after the disappearance of AI in these three patients are summarized in Table III The Group II patients were followed for two years or more and no change was observed in the intensity of the AI murmur

Discussion

When a child has a small VSD and surgical closure has not been recommended, the appearance of aortic insufficiency would prompt a re evaluation of the decision because a relatively benign lesion would have changed into a significant one The severity of the aortic valve insufficiency progresses in these patients and usually operative intervention eventually becomes necessary

The clinical features of VSD with AI are usually characteristic but at times the manifestations are similar to those of such anomalies as ductus arteriosus aorticopulmonary window VSD with pulmonic insufficiency and a fistulous connection of the aortic sinus of Valsalva into the right ventricle [1,3] The incidence of VSD with AI is

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Table I Findings at time of onset of aortic insufficiency

	Group I				Group II		
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (yr) and sex	3 M	4 ½ M	2 M	2 1/6 M	5 M	4 ½ M	5 ½ M
Heart murmur (scale 1 6)							
AI	2/6	2/6	3/6	2/6	2/6	4/6	2/6
VSD	3/6	4/6	4/6	4/6	3/6	4/6	3/6
Blood pressure in right arm (mm Hg)	100/55	106/40	82/30	70/54	92/40	100/58	102/70
ECG	Mild LVH	Mild LVH	Mod. LVH	Mod. BVH	Mild LVH	Mild BVH	Mod. BVH
Chest x ray							
C/T ratio	0 50	0 52	0 55	0 52	0 42	0 55	0 50
PV	+	+	++	++	Normal	++	+
Pressure in ascending aorta (mm Hg)	105/62	109/56	108/42	85/40	120/75	106/63	Not obtained
	m = 75	m = 78	m = 74	m = 55	m = 98	m = 77	

Abbreviations LVH left ventricular hypertrophy BVH, b ntricular hypertrophy C/T cardiothoracic ratio PV pulmonary vascularity

Table II Operative findings and surgical procedure

Case No	Operative findings			Surgical procedure
	Site of VSD	Size of VSD (diameter in mm.)	Aortic valve prolapse	
1	Supracristal	10	RCC	Dacron patch
2	Supracristal	7	RCC with dilated SV	Direct suture
3	Supracristal	6	RCC	Dacron patch
4	Supracristal	unknown	NCC	Direct suture
5	Infracristal	15	RCC and NCC with markedly dilated SV	Dacron patch
6	Infracristal	12	NCC	Dacron patch
7	Infracristal	15	RCC	Direct suture

Abbreviations RCC right coronary cusp NCC noncoronary cusp SV sinus of Valsalva

Table III Postoperative data (Group I)

Case No	Time since VSD closure (yr)	Heart murmur (scale 1-6)	Blood pressure (mm. Hg)	Chest x ray	ECG
1	3	None	105/70	Normal	Normal
2	3	1/6 PFM	120/80	Normal	Normal
3	4	1 6 PFM	80/52	Mild cardiomegaly normal PV	Mild LVH

Abbreviations PFM pulmonary flow murmur PV pulmonary vascularity LVH left ventricular hypertrophy

cause progressive dilation of the anulus and increasing central aortic insufficiency we have considered the appearance of this complication in the supracristal group as an indication for immediate repair of the VSD Indeed some authors have recommended identifying supracristal VSD and the abnormal aortic valve by routine left ventricular angiography and root aortography in all children with VSD and consideration of repair with the indication of potential aortic regurgita



Fig 1 Lateral aortic root angiogram—supracristal VSD Left prolapsing right coronary cusp (arrow) with moderate AI (case 1) Middle, right coronary cusp and right coronary sinus prolapse beyond the normal contour (arrow) with moderate AI Also note small jet from VSD (case 2) Right prolapsing right coronary cusp is displaced downward almost to the level of the bottom of the right coronary sinus (arrow) with moderate AI (case 3)

low, ranging from 3 to 5 per cent in the United States of America[4,5] to 8 2 per cent in Japan[6] The syndrome is more common in male patients[4,7] The murmur of AI appears between the ages of two and eight years[7,8], rarely after eight years

VSD with AI can result from two types of pathologic anatomy In 1968 Van Praagh and McNamara[14] in a morphologic analysis of 11 cases identified two groups based upon the location of the VSD—either superior or inferior to the crista supraventricularis They found that the infracristal type is usually due to deficiency or absence of an aortic commissure and the subpulmonic (or supracristal) type is due to the herniation of the right coronary cusp into the right ventricular outflow tract through the VSD, as a result of hypoplasia of the conal septum VSD with AI seems to occur much more frequently in the relatively uncommon supracristal VSDs[8,9] and, indeed the high frequency noted in Japan appears to be related to a considerably higher frequency of supracristal VSDs in that population group Obstruction of the right ventricular outflow tract is not uncommon in this anomaly and is due to valvular or infundibular pulmonic stenosis or to prolapse of the aortic valve through the VSD[6,14]

There have been different opinions as to the best timing and type of operation for this combined anomaly Several authors[16,18] reported successful cases in which only the VSD was repaired and the AI was not treated—the degree of AI was minimized or eliminated The authors assumed that repair of the VSD alone would correct the AI in part, if not totally Other reports recommended a transaortic approach to repair the VSD and AI either by plication or by homograft[8,13]

Our experience supports the view that, in the presence of a prolapsing aortic cusp in supracristal VSD, simple closure of the VSD is an effective method of eliminating aortic regurgitation, and this is our present recommendation In our three patients the AI murmur disappeared two to three years after VSD repair Kawashima and associates[7] and Plauth and colleagues[3] reported cases analogous to ours All of them had supracristal VSD and the AI was secondary to the herniation of the right or noncoronary cusp through the VSD Closure of the VSD alone in these patients provided sufficient support to the prolapsed leaflet and further restored the aortic valve function If on the other hand the lesion is subcristal, the experiences recently reported by Spencer and associates[13] and supported by Trusler[19] would indicate a highly favorable outlook for plication repair of the involved aortic valve cusps

Because of the above experiences and our concern that continued aortic regurgitation would

The significance of fever in acute myocardial infarction. A reappraisal

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Thirty six years ago Master and associates[1] stated that fever was one of the cardinal signs of coronary thrombosis and a reliable guide to the degree of infarction. Since then little interest has been manifested in the clinical significance of this easily obtained physical finding other than restatements of the above. In 1967 a professional activity study indicated that 27 per cent of 1,921 patients with acute myocardial infarction (AMI) were given antibiotics.[2] These data were obtained from 44 hospitals in North Carolina and there was a range distribution from 12 to 52 per cent for individual hospitals. In a disorder where fever was considered to be an expected finding this was a remarkably high proportion of patients being treated for infective illness presumably heralded by fever. Accordingly, the present study was initiated to re-evaluate the significance of fever in patients with AMI under the controlled and standardized conditions of a coronary care unit.

Materials and methods

One thousand successive patients initially admitted to the coronary care unit were selected for study. Basic criteria for inclusion were (1) time of onset of symptoms could be defined, (2) adequate diagnostic studies were available, (3) regular rectal temperatures had been taken, generally on a four hourly basis. Diagnostic standards for AMI were based on a numerical weighting system (Table I) and for cardiac pain on the Rose[3] questionnaire. According to these criteria 334 patients had acute myocardial infarction, 289 had cardiac ischemia or intermediate syndrome, and 377 others were considered not to have coronary artery disease as their primary presenting feature—these being patients with chest pain, syncope, heart failure, or arrhythmias admitted for diagnosis or treatment. The AMI's were further subdivided into 180 transmural and 154 nontransmural by the presence or absence of abnormal Q waves in serial 12 lead electrocardiograms (ECG).

A normal temperature was defined as a rectal temperature which was less than 38.0° C. For the purpose of identifying point prevalence, fever was defined as a rectal temperature of 38.0° C or more recorded on two successive 24 hour periods during the first seven days of illness. After seven days rectal temperatures were not always taken and data were converted by adding 0.6° C to the oral temperature level. Sputum and urine cultures were taken in patients with a temperature of 38.0° C or more. Only deep sputum specimens not thought to be saliva were used and these were smeared and cultured appropriately. A growth of a specific organism reported as heavy was considered positive evidence of bacterial infection in the presence of a chest x-ray read as demonstrating consolidation or atelectasis. Urinary specimens were clean voided or from closed catheter systems. Significant bacteriuria sufficient to be called an infection was considered to be a minimum of two specimens with a colony count greater than 100,000 bacteria per milliliter of urine. A minimum of six blood cultures was taken in all patients with a temperature of 39° C or more. Patients with previously known chronic urinary or respiratory infections were not included in the infection group unless fever and clinical data indicated an exacerbation.

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tion in those patients having supracristal VSD and an abnormal aortic valve cusp[17]

Our own approach has been to try to identify, within the clinical group of children who have a small VSD, those with potential supracristal ones by the presence of the regurgitant murmur considerably higher along the left sternal border than is usual and then to completely evaluate their cases We do not recommend repair before the onset of AI even when an abnormal aortic valve is noted

Summary

We have described seven patients with aortic insufficiency and ventricular septal defect (classified by Tatsuno and associates[6] as supracristal and infracristal) Four patients (Group I) had supracristal VSD and three (Goup II) had infracristal) VSD All underwent VSD repair only, without operation on the aortic valve In three patients from Group I the AI disappeared two to three years after VSD repair

From our present study and reports of others it is suggested that if the VSD is supracristal appearance of AI is an indication for early surgical repair of the VSD prior to development of signs and symptoms of left ventricular failure with the expectation that AI will disappear or be minimized

We wish to acknowledge the secretarial assistance of Miss Patricia Bonino

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ble for infection with one exception the patient with staphylococcal septicemia The data from this analysis of variables therefore indicated that the group of patients with infection were usually more ill since they had a disproportionate num ber of invasive maneuvers performed for the monitoring of cardiac function

Fever beyond the fourth day By the fifth day 78 (23 per cent) of the patients with AMI had fever of 38 5 C or greater and the infarct was transmural in 64 Table IV shows the related etiologic factors found in this group Nearly half the patients had demonstrable infection and in the remainder myocardial infarction with or without pericarditis diagnosed by the presence of a pericardial friction rub was the commonest concomitant complication It was often difficult to tell whether such a fever was due to extension of the infarct in this group of patients It was also most unusual to be able to attribute fever to pulmonary embolization It was surprising that only one drug reaction was found since patients in our unit take on an average eight drugs spe cifically related to treatment of their acute episode Atropine was used in 39 per cent of the patients with AMI but no evidence was found that this was responsible for high or persistent fever From days 8 to 14 infection or possible in fection was present in the majority of patients with this level of fever The percentage likeli hood based on our data of the presence of infec tion as a cause for various levels of fever during each day of the first seven days of AMI is indi cated in Fig 2 by day 4 a temperature of 39 0 C or more carried a 50 per cent possibility and this increased up to 100 per cent at day 7 These figures give support for the positive attempts that must be made to identify infection at such levels of fever

Maximal temperatures obtained *during first* seven days Table V shows the maximal rectal temperatures during the first week *in patients* with AMI without infection those with infection and those patients with cardiac i chemia only It is most exceptional for fever to exceed 40 unless infection exists Without the presence *of* infec tion the temperature is likely to exceed 39 C *in* only 20 per cent of patients The striking con trast with cardiac ischemia patients is demon strated since only one in 243 had a temperature of 39 C or greater

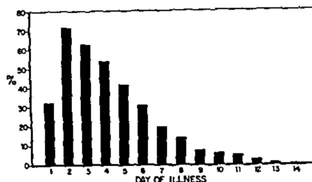


Fig 1 AMI and cardiac ischemia percentage of patients by day of illness with rectal temperature elevation of 38 0 C or more

Table II Type of organism isolated from patients with AMI during first week of illness

	Respiratory	*Urinary*	*Other*
Gram positive cocci			
Pneumonococcus	11	—	—
Staphylococcus	9	—	1
Streptococcus	1	—	1
Enterococcus	—	8	—
Gram negative bacteria			
Enterobacter	7	—	—
Escherichia	2	14	—
Klebsiella	4	3	—
Hemophilus	2	—	—
Pseudomonas	1	2	—
Proteus	—	2	—
Total	37	29	2

Enzyme and white blood count (WBC) correla tions with maximal temperatures Significances were established for correlations between max imal levels of temperature in patients without in *fection* WBC levels, and enzyme data (creatine phosphokinase [CPK] lactic dehydrogenase [LDH] and serum glutamic oxalacetic trans aminase *[SGOT]* that might indicate size of in farction[4] The age of the patient and the type of myocardial infarction were considered Transmural myocardial infarction WBC and enzyme data did not correlate with maximal tem perature levels other than for LDH in patients 70 or over (P < 0 01) Correlations for SGOT and LDH were present for subendocardial infarction

Table I *Weightings for the diagnosis of recent AMI*

1 CLINICAL

A Chest pain

- 4 History of typical chest pain (greater than 30 minutes)
- 2 *History of preinfarction angina only*
- 1 Atypical chest pain only

B Other

- 3 Acute pulmonary edema shock syncope and cardiac arrest with identified major arrhythmia (asystole ventricular fibrillation ventricular tachycardia second degree and/or third degree heart block)
- 3 Death within 48 hours of onset of symptoms
- 2 Congestive heart failure
- 2 *History of previous myocardial infarction or high risk*
- 1 Symptoms of possible arrhythmia palpitation faintness syncope

2 ECG

- 6 Serial acute changes of type identifying transmural AMI
- 4 Changes of marked to extreme acute ischemia (ST depression 0 2 mv or more ± T inversion)
- 3 Changes of minor to moderate acute ischemia (ST depression less than 0 2 mv ± T inversion)
- 2 T inversion only
- 2 New ischemic changes of any degree (ST T) on top of old myocardial infarction pattern
- 2 Left bundle branch block
- 1 Old ischemia or infarct pattern

3 ENZYMES

- 6 *Elevation of both CPK and SGOT simultaneously within 48 hours of onset of major symptom (N B Elevation = X 2 upper limit of normal and should not be associated with other known causes of enzyme elevation)*
- 3 Elevation of LDH within period of 48 to 72 hours of onset of major symptom
- 1 Elevation of either CPK or SGOT when both obtained simultaneously

4 AUTOPSY

- 10 Autopsy changes of AMI

Add sum of weightings for sections 1 to 4 Only one (maximal) weighting per section

If 10 or more points are scored, the diagnosis is recent AMI

If less than 10 are scored, recent myocardial infarction is unlikely

Results

Incidence and prevalence of fever Fig 1 shows *the daily incidence* of fever, as defined for the total cohort of patients with AMI During the first 24 hours 32 per cent *had fever and during* the next 24 hours the maximal incidence of 72 per cent occurred During days 3 to 9 there was a linear fall and by day 10 only 7 per cent of patients had fever by day 14 fever was most uncommon

The seven day point prevalence of fever for various categories of patients in the coronary care unit was established. It was found that 218 (65 3 per cent) of the 334 patients with AMI had fever and that this was more common in transmural (77 2 per cent) than nontransmural (50 7 per cent) myocardial infarction This was in contrast to the 289 patients with cardiac ischemia of whom only 6 6 per cent had fever In the 377 remaining patients, permanent pace*maker insertion and other diagnostic problems* related to chest pain or cardiac failure were the commonest associated diagnostic categories for the 23 6 per cent who had fever

Concomitant infections in AMI There was an over all incidence of 18 9 per cent of patients with AMI who had positive cultures considered to be significant and therefore responsible for fever *This was in contrast to* patients with cardiac ischemia in whom positive cultures were found in only 1 4 per cent. Similarly there was a lower in*cidence (6 4 per cent) in patients with* other problems In AMI the clinically identified site of infection was in the respiratory (9 per cent) or urinary tract (6 9 per cent) *or a combination* of both (? 4 per cent) The remaining two infections (0 6 per cent) were a staphylococcal septicemia *and a* streptoccal pharyngitis The types of organisms isolated are shown in Table II and it can be seen *that gram negative bacteria were* frequently found Pneumococcus was common in respiratory tract infection and Escherichia in urinary tract infection No unusual organisms were isolated and no fungi were identified

In order to determine whether *there* was a difference between the patients who had infection and the remaining cohort, certain possibly *associated variables were considered* (Table III) A positive chest x ray whether due to pulmonary vascular congestion consolidation and/or atelectasis was *significantly present more often* in patients with *infection* The utilization of urinary catheters was much more *common in* the infected group (P < 0 0005) as was the utilization of central venous pressure catheters *(P < 0 0005)* There was no significant difference in the use of temporary pacemaker catheters There was no evidence that central venous pressure or temporary pacemaker catheters were directly responsi

Table V Maximal rectal temperatures recorded during first week in patients with AMI subdivided into those with and without infection and cardiac ischemia

Temperature (C)	*AMI infection*		*AMI no infection*		*Cardiac ischemia*	
	n = 63	%	*n* = 271	%	*n* = 289	%
< 38 0	1	1 6	66	24 4	243	84 1
38 0 38 9	24	38 1	151	35 7	45	15 6
39 0 39 9	29	40 0	52	19.2	1	0.3
40 0+	9	14 3	2	0 7	0	0 0

Table VI AMI 28 day mortality rate by age and presence or absence of infection

Age	*Total*		*Infection*		*No infection*		χ^2	*P*
	No	%	*No*	%	*No*	%	*(df = 1)*	
70+	34/115	29 6	24/89	27 0	10/26	38 5	1.28	< 0 5
< 70	24/219	11 0	19/182	10 4	5/37	13 5	0 30	< 0 75
Total	58/334	17 4	43/217	15 9	15/63	23 8	2 25	< 0 25

are liable to develop respiratory or urinary infection frequently due to gram negative organisms The gram negative bacteria isolated from sputum are strikingly similar in type and frequency to those in the study made by Johanson and colleagues[5] in which they described the rapid appearance of such organisms in the upper respiratory tract in hospitalized patients They felt that bacterial pneumonia began with the aspiration of such organisms into the lung from the upper respiratory tract and that the appearance of gram negative organisms in pharyngeal flora might represent an important step in the pathogenesis of pneumonia due to gram negative organisms in any form of acute illness. AMI may be no exception The use of indwelling catheters which was so frequent in our patients could easily lead to a high incidence of urinary infection

If a fever of 38 5 C or more persists in a patient with AMI beyond the fourth day then an aggressive policy of searching for infection is mandatory If infection does not exist then a common relationship for such a fever would appear to be pericarditis as reflected by a pericardial friction rub heard usually before the fourth day This finding might indicate that the fever was a manifestation of an early Dressler s syndrome In this series it was exceptional to find patients with acute pulmonary embolization although it might be that this complication was not recognized clinically Nevertheless an attempt was made to be sure that this diagnosis was always considered. A large proportion of our patients were receiving anticoagulant therapy (61 per cent) and early ambulation is the rule in our unit. This may be the reason for the few patients with pulmonary embolization This is in contrast to older series, where pulmonary embolization was considered to be an important cause of fever[6]

Mortality data are difficult to analyze since patients were treated aggressively with appropriate antibiotic therapy for their infection and this

Table III AMI certain variables that might be associated with infection contrasted with their presence in uninfected patients The P values indicate the significance of the difference

Variables	*Infection (n = 63)*		*No infection (n = 271)*		x^2 *(df = 1)*	*P*
	No	*%*	*No*	*%*		
Positive chest x ray	40	63 5	117	43 2	8 47	< 0 005
Urinary catheter	35	55 6	45	16 6	42 47	< 0 0005
Central venous pressure catheter	22	34 9	34	12 5	18 34	< 0 0005
Pacemaker catheter	8	12 7	26	9 6	0 54	< 0 5

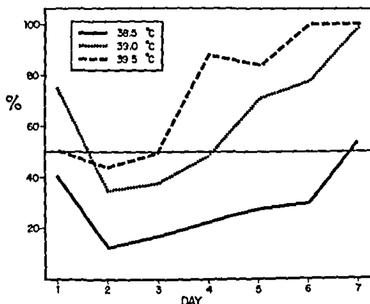


Fig 2 AMI and cardiac ischemia probability by percentage of the presence of infection by day for certain levels of rectal temperature

Table IV AMI diagnostic categories for patients with rectal temperatures of 38 5° C or more beyond day 4

Diagnosis	*Day*		*Deaths*
	5 7	*8 14*	
Infection	34	14	7
? Infection	7	3	–
AMI only	20	2	–
AMI pericarditis	12	3	1
Embolus	4	–	1
Drug reaction	1	–	–
Total	78	22	9

in patients below the age of 70 (P < 0 01) No correlation between degree of fever and WBC level was present

Mortality Table VI shows the 28 day mortality rate by age in patients with infection vs noninfection The mortality data are acceptable for a coronary care unit and do not reflect any marked deviation from what might be expected There was a difference in mortality figures between patients who are not infected and those who are infected, but this was not statistically significant If the patient groups are divided into those aged 70 and above or those below 70 years there was still no significant difference in the death rate

Discussion

The results of this study demonstrate that fever is very common in AMI and is indeed a cardinal finding as Master stated Excluding infection AMI gives rise to fever which is most common on day 2 rarely exceeds 39 5° C or persists beyond day 8 and is more often seen in patients with transmural infarction as opposed to subendocardial infarction Fever is rare in the intermediate syndrome of coronary disease or cardiac ischemia Correlative data support the concept that the degree of fever unrelated to infection in AMI is not associated with the mass of myocardium involved It is probably a nonspecific pyrogenic reaction requiring only a relatively small critical mass of infarcted tissue

In view of the commonness of infection in the course of AMI possible precipitating factors should be considered in order that appropriate preventive therapy may be employed Those patients who have more than mild cardiac failure

The prediction of maximal oxygen consumption from a continuous exercise treadmill protocol

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Initially treadmill exercise protocols were designed to accurately measure maximal oxygen consumption [1-4] Interrupted work loads of progressive intensity were used to determine the greatest oxygen consumption that a subject could attain Subsequently, more convenient continuous treadmill protocols were devised.[5,6] Recently we have presented data which show that comparable results can be obtained with both types of tests

Maximal oxygen consumption which is equal to maximal cardiac output times maximal AV O_2 difference can be used clinically to estimate the performance of the heart as a pump Since maximal AV O_2 difference does not differ much under similar circumstances maximal oxygen consumption is a linear estimate of maximal cardiac output [1]

Physical training and cardiovascular function are two of the factors that effect maximal oxygen consumption [8,9] Balke attempted to isolate the effect of physical training to estimate physical fitness by testing only healthy men while Bruce has attempted to isolate cardiovascular functional performance by considering sedentary and active men separately [10,11] Both Balke and Ware[5] and Bruce and associates[10,11] have proposed nomograms for estimating maximal oxygen consumption from maximal treadmill time These nomograms are for the practical application of treadmill testing in situations where the equipment for gas analysis is not available Bruce's nomograms are designed to determine the functional aerobic impairment of individuals by adjusting for age The clinical usage of such nomograms is dependent upon how well maximal oxygen consumption can be estimated by maximal treadmill time The purpose of this paper is to evaluate the hypothesis that an individual's maximal oxygen consumption can be realistically estimated from a continuous progressive treadmill protocol

Methods

Treadmill testing was performed in the morning with subjects fasting This was their first experience at treadmill walking They were not allowed to support their weight on the handrails Treadmill speed was constant at 3 3 m p h (90 M per minute) and the grade was increased 1 per cent every minute The electrocardiogram (ECG) was monitored continuously during exercise and for eight minutes after exercise The subjects were urged to give a maximal effort However during the first quarter of the study arbitrary heart rate limits of 200 and 180 were inconsistently imposed for the special project candidates and the normal consults, respectively There after no heart rate limits were imposed The treadmill used had a grade limit of 22 per cent so data from 55 men who exceeded 22 minutes of treadmill walking were considered separately

Expired air was collected by means of a standard mouthpiece and nose clip Collins triple J valve and neoprene balloons during the final

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may have improved the prognosis In addition, a reverse possibility exists in that infection was as sociated with more aggressive intervention in severe myocardial infarction which already had a worse prognosis An appreciation that deaths and morbidity from infection in patients with AMI may be lessened is appropriate but it is not ethically possible to perform control experiments in order to obtain relevant statistical data All that can be stated is that with therapy for infec tion there was no statistically significant excess mortality rate in that group

The management of patients with AMI has reached a refinement hitherto unknown mainly due to a new attitude towards arrhythmias Nonetheless the prevention recognition, and treatment of infection form an additional area that has to be considered in the aggressive man agement of the patient with AMI, for this is a complication not to be ignored Prompt recogni tion and treatment of cardiac failure, avoidance of oversedation pulmonary therapy to eliminate atelectatic areas and a conservative attitude to the use of indwelling urinary catheters are all necessary in order to prevent infection

Summary

A reappraisal of the significance of fever in acute myocardial infarction was undertaken in the controlled environment of a coronary care unit With the use of standardized criteria, 334 patients were given a diagnosis of acute myocar dial infarction The seven day point prevalence for fever was 65 3 per cent with a maximal inci dence of 72 per cent on the second day No signifi cant correlation could be found between max imal temperature levels degree of enzyme eleva tion and leukocyte count A policy of making cul tures from those patients with fever identified in fection in 63 (18 9 per cent) with a high correla tion in this group with heart failure, atelectasis and the use of urinary and central venous pressure catheters High fever or fever beyond the fourth day of illness was most likely caused by respiratory or urinary tract infection fre quently related to gram negative organisms. These data reinforce the commonness of fever but also indicate that the prevention, recogni tion and treatment of infections should be an im portant part of the management of patients with acute myocardial infarction

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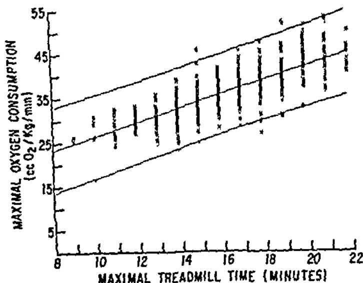


Fig 1 Regression line with (0 95 0 95) tolerance limits based on 1 025 normal men exercised using the Balke protocol

and the remaining 22 per cent for minor medical problems or to rule out erroneous diagnoses The age range was from 20 to 53 years

In order to check the air collection technique and to analyze the oxygen consumption and heart rate approaching maximum an additional 127 men were studied. No heart rate limits were set and multiple full minute bags of expired air were collected prior to maximum. Their data were considered separately

Results

Balke s nomogram was constructed with data from subjects who exercised to a heart rate limit of 180 therefore our study group was divided into two subgroups One subgroup included only those who exercised to a heart rate of 180 or less, while the other consisted of those who exercised to higher heart rates Table I lists the mean with its standard deviation for each physiologic parameter in the total group the two subgroups and in the separate group with multiple air bag collections

For each group maximal oxygen consumption was linearly regressed against maximal time with the use of a least squares fit regression technique Table II shows the regression equations for the groups with standard error of estimates and correlation coefficients Fig 1 represents the relationship of maximal treadmill time and maximal oxygen consumption with the (0 95 0 95) tolerance limits for the 1 025 normal men The tolerance limits are constructed such that one can be 95 per cent confident that at least 95 per cent of future observations from the same population will fall within the limits

Table III compares the data from the groups of individuals whose maximal treadmill time was 10 15 and 20 minutes The mean maximal oxygen consumption can be compared to the values estimated by the computed regression lines Also the (0 95 0 95) tolerance limits computed from the regression analyses can be compared.

Table IV shows the mean heart rate and oxygen consumption during the last minute and the minute before maximal time for the 127 subjects who had multiple air bags collected. The mean difference between these two times was determined and there was a significant difference ($P < 0.001$) for both heart rate and oxygen consumption Only 22 per cent of these subjects showed an absolute plateauing of oxygen consumption 13 per cent showed a plateauing of heart rate and 3 8 per cent showed a plateauing of both parameters There were no inconsistent measurements approaching maximal time and the final minute was valid for determining maximal oxygen consumption

Fifty five (5 1 per cent) of the total group of men walked for longer than 22 minutes. In spite

Table I Mean with standard deviation for each of the physiologic parameters of the four study groups

Group	Age (yr)	Maximal oxygen consumption (c c O_2/kg /min.)	Maximal treadmill time (min.)	Maximal heart rate
Total group of 1 025 men	34 2 (7 2)	36 15 (6 13)	16 5 (2 9)	186 1 (10 8)
Subgroup with heart rate of 180 or less (N = 317)	37 2 (7 5)	34 11 (5 77)	15 3 (2 8)	173 6 (7 1)
Subgroup with heart rate greater than 180 (N = 708)	32 8 (6 6)	37 07 (6 07)	17 1 (2 8)	191 7 (6 8)
Group with multiple air bag collections (N = 127)	38 0 (9 0)	36 74 (5 58)	15 2 (2 9)	183 3 (10 7)

Table II Equations for the regression lines of maximal oxygen consumption plotted against maximal treadmill time in the four study groups (r = correlation coefficient, S E = standard error of estimate)

1 Total group of 1 025 men
Maximal oxygen consumption = 11 12 + 1 51 (maximal treadmill time) S E. = 4 26 r = 0 72

2 Subgroup of 317 men with heart rate of 180 or less.
Maximal oxygen consumption = 11 29 + 1 49 (maximal treadmill time) S E. = 3 92 r = 0 74

3 Subgroup of 708 men with heart rate greater than 180
Maximal oxygen consumption = 11 25 + 1.51 (maximal treadmill time) S E. = 4 41 r = 0 69

4 Group of 127 men with multiple expired air bags collected
Maximal oxygen consumption = 11 19 + 1 70 (maximal treadmill time) S E = 2 84 r = 0 87

minute of exercise Gas volume measurements were made with the use of a Tissot correcting for pressure and temperature Carbon dioxide was measured by a Beckman LB 1 and oxygen by a Beckman E 2 The gas analyzers were calibrated daily with gases analyzed with the Micro Scholander technique One hundred three randomly selected samples of expired air were tested simultaneously with the Beckman instruments and the Micro Scholander technique to check for accuracy

The data collected on 1 800 men consecutively studied at the United States Air Force School of Aerospace Medicine (USAFSAM) were reviewed Men with any of the following findings were excluded from further analysis (1) those with symptoms or findings of cardiovascular disease or any ailment that could limit treadmill performance (2) those with a submaximal treadmill effort as judged by those monitoring the tests and by review of the data and those with a maximal RQ less than one (3) those with resting ECG abnormalities such as bundle branch blocks repolarization abnormalities, and abnormal Q waves (4) those with resting blood pressures consistently above 140/90 mm Hg as well as labile hypertensives and (5) those with abnormal ECG responses to maximal treadmill testing or a double Master s test

The 1,080 men who remained were judged to be free of systemic and cardiovascular disease after a thorough medical and cardiovascular workup Thirty per cent of these men were referred for evaluation as special project candidates 15 per cent for ophthalmologic and otolaryngologic problems 14 per cent for syncope or near syncope 10 per cent for neurologic evaluation 9 per cent for psychiatric problems

Table IV Data from the 127 subjects with multiple expired air bags collected

	Minute prior to maximal time	Last minute of treadmill exercise	Mean difference	Standard error
Heart rate	178 6	183 3	4 7	0.33
Oxygen consumption ($cc\ O_2$/Kg /min.)	34 76	36 74	1 98	0 22

one fifth of the subjects consistent with our previous findings[7] The maximal and maximal minus one minute values were significantly different (P <0 001)

A previous study showed that treadmill experience could increase treadmill performance time without an increase in maximal oxygen consumption[7] This effect was avoided by considering subjects with no previous treadmill experience Submaximal oxygen consumptions measured at 10 and 15 minutes in the Balke protocol during the previous study (Table V) can be compared to maximal oxygen consumption for individuals whose maximal treadmill times were 10 and 15 minutes This comparison suggests that those exercising maximally at these times are less efficient than those exercising submaximally

It appears that the maximal performance time in a continuous progressive treadmill protocol can only grossly predict maximal oxygen consumption Thus the accurate determination of an individual s functional aerobic capacity or the indirect estimate of maximal cardiac output requires the actual measurement of oxygen consumption

Summary

This study investigated the hypothesis that an individual s maximal oxygen consumption can be realistically predicted by the maximal time achieved in the Balke treadmill protocol The oxygen consumption in the final minute of exercise of 1 025 normal men who performed a maximal effort in the Balke protocol were linearly regressed on their maximal treadmill time using a least squares fit technique In addition the men were grouped by heart rate response and regression equations plus (0 95 0 95) tolerance limits were computed for each subgroup A regression equation was also computed for an additional 127 men who had multiple bags of expired air collected approaching maximal effort. It was demonstrated that the tolerance limits are so wide that maximal oxygen consumption can be only grossly estimated by treadmill time Thus other factors than maximal oxygen consumption must be operating in determining treadmill performance

Table V Submaximal oxygen consumption of 15 subjects whose maximal treadmill time exceeded 15 minutes during their first treadmill walk

Treadmill time (min.)	Mean oxygen consumption with standard deviation ($cc\ O_2$/Kg /min.)
10	24 30 (2 0)
15	32 6 (2 5)

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Table III Comparison of the derived regression analyses in the groups

Group	Maximal treadmill time (min)	No of subjects	Mean maximal oxygen consumption (c.c O_2/kg/min.) (with standard deviation)	Estimated maximal oxygen consumption from regression line	(0 95 0 95) tolerance limits
Total group of 1 025 normal men	10	12	27 61 (4 31)	26 26	16 64 35 88
	15	111	34 01 (4 23)	33 83	24 69 42 97
	20	87	41 57 (5 13)	41 40	32 11 50 70
Subgroup of 708 men with maximal heart rates greater than 180	10	4	29 60 (3 39)	26 35	15 99-36 72
	15	79	34 35 (4 40)	33 90	24 21 43 59
	20	68	41 32 (5 23)	41 45	31 67 51.22
Subgroup of 317 men with maximal heart rates of 180 or less	10	8	26 61 (4 56)	26 24	16 64 35 83
	15	32	33 18 (3 70)	33 71	24 [illegible]8-4[illegible] 64
	20	19	42 44 (4 78)	41 18	31 68 50 68
Group with multiple air bag collections (N = 127)	10	3	30 03 (1 38)	28 21	20 41-36 01
	15	19	36 08 (2 15)	36 72	29 67-43 78
	20	4	45 57 (4 26)	45 23	37 51 5[illegible] 95

of walking anywhere from 23 to 44 minutes, their mean 'maximal' oxygen consumption was approximately 45 c c of O_2 per kilogram per minute This is the approximate mean aerobic cost of performing the 22nd minute of the Balke protocol and was consistent with the 22 per cent grade limit of the treadmill

The simultaneous determinations of maximal oxygen consumption with the Beckman instruments and the Micro Scholander technique showed a correlation coefficient (r) of 0 97

Discussion

This study demonstrates that the maximal oxygen consumption can differ widely among individuals for any maximal treadmill time There is too much overlap of the range of maximal oxygen consumption for maximal treadmill times to accurately separate those with different aerobic capacities except in a very gross fashion Apparently other factors than maximal oxygen consumption are operating in determining the treadmill performance of an individual

Balke based his nomogram for predicting maximal oxygen consumption on his test performed with a heart rate limit of 180 since he felt that maximal oxygen consumption was achieved by this heart rate limit [5] However early in this study one of the present authors (M L) noted that this was not so and removed any heart rate limitations The regression equations for the two heart rate subgroups did not differ significantly (Table II)

The group with multiple air bag collections confirmed the accuracy of the expired air collection techniques There was no inconsistent measurements approaching maximal time and the final minute was valid for determinin" maximal oxygen consumption Plateauing of oxygen consumption at maximal effort was found in only

Experimental and laboratory reports

Severe stress cardiopathy in pigs

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Ample evidence has been obtained in rats that cardiac lesions can be produced by exposure to various types of stress ("simple stress cardiopathy") The lesions produced by restraint stress are of minor functional importance, disappear without leaving a trace and are rarely detected in clinical pathology [19] In dogs "restraint stress" produced activation of the adrenal cortex but attention has been focused on the central mechanisms involved in transmission and modification of the stressing stimuli [5,6] the myocardium has not been investigated

Sudden death is not exceptional among pigs handled for slaughter [13] dyspnea hyperthermia and cyanosis are leading symptoms and general stasis and intramural subendo and subepicardial hemorrhages are revealed at necropsy [3]

Evidence is accumulating that the cardiovascular system in pigs is more comparable to that of man than is that of the animals (rats and dogs) mainly used for cardiovascular research [9,15] No attempt has been made however to investigate stress induced cardiopathy in pigs

The aim of the present study was to investigate whether "restraint stress (prevention of escape behavior by myorelaxant) under controlled experimental conditions can produce cardiac lesions in pigs Results obtained have shown that this procedure can produce severe cardiopathy—in several cases lethal.

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Material and methods

A total of 32 crossbred pigs of Yorkshire and Swedish landrace (body weight 85 to 90 kilograms age six months) of both sexes was used. Four experimental series were studied successively as the results in all were the same they are presented together

To produce restraint stress in pigs 23 animals were taken into the experimental room where they were adapted for at least 15 minutes (acclimatization) Synthetic short acting peripheral muscle relaxant (Celocurin Vitrum succinylcholine chloride) was injected intravenously in repeated doses (0 14 mg per kilogram of body weight) within 15 to 20 minutes (relaxation period) Muscle relaxation was achieved without respiratory distress (blood gas analysis controls Pco_2 35 to 46 pH 7.35 to 7 43 Po_2 75 mm Hg animals treated by myorelaxant Pco_2 28 28 Po_2 81 80 pH 7 43 to 7 46) Relaxed animals were stimulated by a standard electric animal pusher (in spike 6 000 v 1 microamp) on the dry skin surface of the hind leg five to six times during 15 to 20 minutes (relaxation + stimulation period) The electrocardiogram (ECG) was recorded (Elema Schonander 42 B) in acclimatization relaxation and relaxation + stimulation periods by using silver clip electrodes placed as extremity and precordial leads Animals which survived were put to death 24 to 48 hours after the experiment by bolt pistol (immediate death by mechanical brain destruction)

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Table I Summary of results obtained in 23 experimental animals by ECG recordings, autopsy, and light microscopic examination of heart muscle

Total no of experimental animals	23
Died during experiment	3/23
Survivors	20
Controls	9
ECG changes	
Sinus bradycardia	
Ac*	–
Rx*	2/23
Rx + stim	5/23
Ventricular tachycardia	
Ac	–
Rx	1/23
Rx + stim	14/23
Sinus arrest ventricular *bradycardia*	
Ac	–
Rx	–
Rx + stim	2/23
ST T changes	
T wave inversion	
Ac	3/23
Rx	21/23
Rx + stim	23/23
ST segment lifting	
Ac	–
Rx	1/23
Rx + stim	6/23
Macroscopic changes	
Hemorrhages	
subepi subendocardial and intramural	17/23
Pale areas	9/23
Microscopic changes	23/23

Ac acclimatization rx relaxation stim electrostimulation

Serving as controls were nine animals of the same race and age not treated and put to death by bolt pistol within the animal room

Macroscopic diagnosis was performed by dissecting the myocardium and coronary vessels For histologic examinations multiple tissue blocks were taken from various parts of the left and right ventricles These tissue blocks were fixed in 10 per cent neutral formol and in Gendre's solution for glycogen stain Other tissue blocks were quick frozen in a cryostat for succinic dehydrogenase reaction[16] The fixed tissue was embedded in paraffin and cut into 3 μ thick sections The sections were stained with hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin (PTAH), Masson's trichrome, and von Kossa's stain Sections were also stained with periodic acid-Schiff (PAS) with and without diastase, Goldner's trichrome and reticulum stain In order to identify early myocardial degeneration, the acid fuchsin technique according to Poley and associates[17] was used.

Results

Observations during experiments ECG heart rate, and body temperature Of all animals subjected to "restraint stress" three died—two during the experimental period and one three hours later Only the latter death was preceded by dyspnea and cyanosis, the two other sudden deaths occurred without any noticeable accompanying symptoms The body temperature (rectal and muscle) did not show any significant differences during the experimental period, although a tendency to rise was observed The heart rate did not change in the relaxation period (average in the acclimatization period, 84 per minute, average in the relaxation period, 88 per minute), but a rise was observed after the animals had been stimulated (average 118 per minute) Mean heart rate values are, however, misleading because of different kinds of arrhythmias.

As can be seen from Table I all experimental animals had T wave inversion during the relaxation + electrostimulation period and in three animals T wave inversion was observed during the preparatory phase (acclimatization period) Transitory lifting of ST segment was observed in six of the animals in the relaxation + stimulation period and in one also during the relaxation period. In one of them it was combined with a negative T wave which was still present six hours after the experiment. This animal which was put to death 48 hours after the experiment had a large pale area comprising a great part of the posterior wall of the left ventricle (see Fig 1) The most frequent arrhythmia was ventricular tachycardia (in 14 animals during the relaxation + electrostimulation period and in one animal during the relaxation period) In two cases sinus arrest with ventricular bradycardia was present and in five cases sinus bradycardia was seen, two of them terminating in ventricular standstill and death of the animals—in one case preceded by ventricular fibrillation



Fig 1 Heart of a pig (dorsal view) to which restraint stress was applied 48 hours before the animal was killed. Large necrotic area in the posterior part of the left ventricle (N) Subepicardial hemorrhage (h) Fatty tissue along coronary vessels (f)



Fig 2 Left ventricular free wall of pig myocardium 24 hours after restraint stress Large parts of the wall are necrotized (dark) Endocardium is seen in the lower part of the picture (Goldner's trichrome × 17)

Necropsy findings In the three animals that died spontaneously multiple intramural subepi and subendocardial hemorrhages were seen. Coarse tigroid pale areas were observed mainly in the papillary muscles of the left ventricle

In the 20 animals which were killed 24 to 48 hours after the experiment a large well circumscribed pale area comprising a great part of the posterior wall of the left ventricle was found in one heart (animal killed 48 hours after the experiment) and in five other animals analogous changes but of smaller size were observed.

In 14 hearts multiple small subendocardial hemorrhages in the left ventricle were seen mainly marked on the papillary muscles and the trabeculae carneae Subendocardial hemorrhages were also observed in the right ventricle in three of the 23 specimens.

Microscopic examination Myocardial degeneration and necrosis were found in all 23 hearts examined However the myocardial damage was variable in extent only a few scattered foci of fuchsinophilic degeneration and necrosis were found in some whereas in others

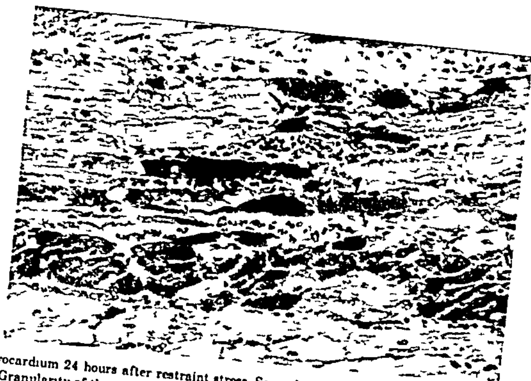


Fig 3 Pig myocardium 24 hours after restraint stress. Several myocardial cells exhibit disruption of the cell architecture Granularity of the cytoplasm (Goldner s trichrome × 320)



Fig 4 Pig myocardium 24 hours after restraint stress. The regular pattern of cross striation is disrupted by transverse bands in the cytoplasm and intervening granularity In other portions (right half of the picture) the cross striation is visible Pyknotic muscle cell nuclei are seen at the top of the picture (Glutaraldehyde fixation post fixed in osmium epon embedded 1μ section toluidine blue × 1 600)

most of the tissue samples from the left ventricle revealed multiple necrotic foci or confluent ne crosis occupying a large part of the wall (Fig 2) The damaged muscle cells were found anywhere in the wall of the left ventricle but were most prominent in the inner third of the wall particu larly in the papillary muscles Sparse myocardial necroses with the same distribution were also found in the right ventricle

Many foci were minute, consisting of only one or two muscle cells Other foci were composed of several cells, some measuring 1 mm in diameter (Fig 3)

The myocardial cell cytoplasm in the degener ated myocardium showed loss of cross striation segmentation and fine or coarse granular disin tegration (Fig 4) There was marked reduction of succinic dehydrogenase in the degenerated myocardium Early myocardial degeneration showed positive reaction with acid fuchsin The



Fig. 5 Pig myocardium 24 hours after restraint stress The dark muscle fibers are Schiff positive after diastase digestion There is beginning proliferation of histiocytes and fibroblasts (Periodic acid Schiff × 400)

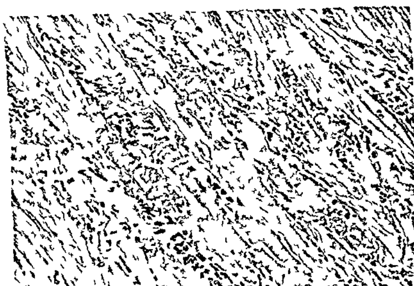


Fig 6 Pig myocardium 48 hours after restraint stress Most of the muscle cells show segmentation and granular disintegration of the cytoplasm There is proliferative cellular reaction of the interstitial stroma. (Hematoxylin and eosin × 370)

foci of necrosis often contained, in addition to the muscular debris accumulations of a homogenous material positive to PAS (Fig 5) Scattered polymorphonuclear leukocytes were seen but were never a prominent feature Proliferative cellular reaction was evident in the interstitial stroma of the injured myocardial cells the reaction being more prominent in animals killed after 48 hours The cells were histiocytes and proliferating fibroblasts (Fig 6) Microscopic examination of heart muscle samples taken from control animals did not reveal any pathologic changes No vascular changes were found in either experimental or control animals

Discussion

In rats cardiomyopathy produced by simple stress in the absence of any special conditioning factor is of only minor functional importance The lesions themselves are rarely visible

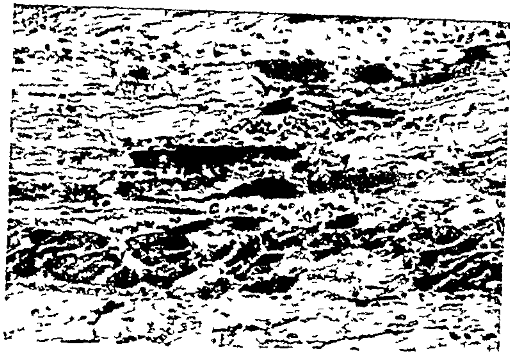


Fig 3 Pig myocardium 24 hours after restraint stress Several myocardial cells exhibit disruption of the cell architecture Granularity of the cytoplasm (Goldner's trichrome × 320)

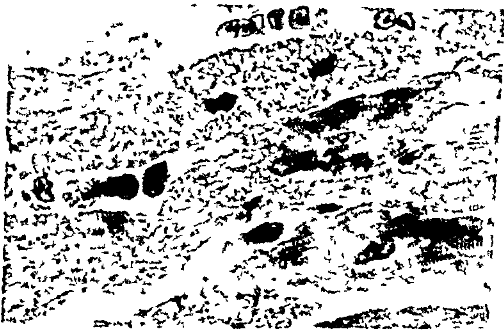


Fig 4 Pig myocardium 24 hours after restraint stress The regular pattern of cross striation is disrupted by transverse bands in the cytoplasm and intervening granularity In other portions (right half of the picture) the cross striation is visible Pyknotic muscle cell nuclei are seen at the top of the picture (Glutaraldehyde fixation post fixed in osmium epon embedded 1μ section toluidine blue × 1 600)

most of the tissue samples from the left ventricle revealed multiple necrotic foci or confluent necrosis occupying a large part of the wall (Fig 2) The damaged muscle cells were found anywhere in the wall of the left ventricle but were most prominent in the inner third of the wall particularly in the papillary muscles Sparse myocardial necroses with the same distribution were also found in the right ventricle

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to the naked eye and histologically they are manifested as scattered necrosis of individual muscle fibers or small fiber groups which heal without leaving a trace[19] This conclusion was derived from experiments performed on young rats mainly females (weight 100 to 200 grams) In contrast to these results the present study has shown that a simple stress procedure in pigs (prevention of escape behavior by temporary restraint by myorelaxant) produces severe cardiopathy accompanied by sudden death in 13 per cent of the cases These experiments substantiate general veterinary experience concerning sudden death in pigs subjected to the stress connected with industrial handling[13]

Distinct macroscopic findings of myocardial damage (pale areas) were not rare in the animals that died The size and severity of the lesions seemed to increase with the lapse of time after stress exposure A uniform microscopic picture of acute cardiac cell damage was disclosed in all animals belonging to the experimental group (fragmentation granulation, and necrosis of the heart muscle cells proliferation of histiocytes and fibroblasts slight polymorphonuclear infiltration) The lesions were located mainly in the inner part of the left ventricular wall especially in the papillary muscles They were similar to those produced by applying catecholamines cobalt or temporary coronary occlusion[1,2,4,7,8,21] Upon macroscopic examination subendocardial hemorrhages were seen to be more common than pale areas (17 animals) Similar hemorrhages combined with myocardial necrosis were observed in dogs after high doses of epinephrine and norepinephrine[14,15,20] Subendocardial hemorrhages were also observed in dogs after electrostimulation of ganglion stellatum[10 2]

The most prominent ECG changes were observed during the period in which electrostimulation was applied to the restrained animals (T wave inversion in all animals and ventricular tachycardia in 14 out of 23 animals)

Because cardiotoxic effects of Celocurin chloride were not reported in the available literature the cardiac lesions described in the present article could not be interpreted as a direct effect of the drug itself It is therefore presumed that the [illegible]cardium of pigs is more sensitive to stre[illegible]s than is that of animals usually used for stre[illegible] experiments (rats) In this connection is to be [illegible]pt in mind the fact that coronary vessels and their peripheral ramifications in pigs are more similar to man than are those of other experimental animals The same holds for fat depots (subcutaneous fat layer)

Recent preliminary observations by the authors have shown that surgical destruction of certain regions in the central nervous system, causing reshape of animal behavior, can prevent this type of cardiac lesion These observations indicate a need for further investigation of the role played by the central nervous mechanisms in the cardiac lesions described.

Summary

In 23 healthy young pigs stress was produced by preventing escape behavior by pharmacologic restraint (Celocurin chloride) In comparison to nine control animals, severe acute cardiopathy was observed in all experimental pigs. In 13 per cent of the animals sudden death occurred. By histologic examination fragmentation granulation, and necrosis of cardiac cells with interstitial reaction developing within 24 to 48 hours was found in all stress subjected animals. Major ECG changes were T wave inversion arrhythmias and transitory lifting of the ST segment. Results are discussed from a comparative point of view A much higher sensitivity of the myocardium of the pig in comparison to that of the rat or the dog usually used in stress experiments is presumed

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Mendez[16] have reported that differences exist in the sensitivity of different glycosides to the antiarrhythmic effects of adrenal vein ligation and acute sympathectomy Furthermore Levitt and Roberts[18] have found that while catecholamine depletion by reserpine is effective against arrhythmias produced by ouabain deslanoside and digitoxin it failed to alter the dose of digoxin required to induce rhythm disturbances These findings point to the need to study more than a single digitalis material to assess the efficacy of a particular drug or experimental procedure as an antiarrhythmic measure For this reason both ouabain and digoxin were used to induce ventricular arrhythmias

Methods

Adult cats of both sexes (2 to 3 kilograms) were anesthetized with Dial Urethane (0 6 ml. per kilogram of body weight intraperitoneally) the trachea was cannulated to insure a patent airway but the animals were not artificially ventilated. The vagus nerves were not sectioned. A femoral artery and vein were cannulated to record blood pressure and to administer drugs respectively A rectal probe connected to a Yellow Springs Telethermometer was used to monitor body temperature which was maintained at 37 C by means of a hot water pad (K Aquamatic) Lead II of the electrocardiogram (ECG) was monitored to determine heart rate and to detect changes in rhythm The ECG and blood pressure were recorded on a Grass polygraph throughout the experiment. Practolol hydrochloride* was dissolved in saline and was given at a rate of 2 mg per kilogram per minute until a total dose of 4 mg per kilogram was achieved This dose was selected since in our previous work it was found to be the dose necessary to protect against digitoxin induced arrhythmias [15] This dose is greater than that required to produce beta blockade [14] Sotalol† was used as the hydrochloride and was also dissolved in saline and administered at a rate of 0 5 mg per kilogram of body weight per minute to a total dose of 2 mg per kilogram of body weight. This dose is approximately the same as that used by other investigators in their exploration of the antiarrhythmic effects of this agent in digitalis induced arrhythmia[4] and thus allows for comparisons to be made between our studies and those of other researchers This dose is referred to as the low dose in the text In three cats sotalol was also administered in a total dose of 10 mg per kilogram of body weight before the infusion of ouabain This dose is referred to as the high dose in the text. Both doses of sotalol are considerably larger than that needed to produce beta blocade [19] The dose of the drugs refers to their respective salts

Either sotalol or practolol was administered intravenously 15 minutes prior to the start of the glycoside infusion

Digoxin (Lanoxin) and ouabain* (ouabain octahydrate Lilly) were dissolved in saline and administered intravenously at 2 μg per kilogram of body weight per minute by means of a constant rate infusion pump The time and dose of the glycoside necessary to produce premature ventricular contractions (PVC) sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) were determined. The dose and time of glycoside necessary to produce PVC VT and VF in the control and drug treated group were compared by Student s t test P values of 0 05 or less were considered significant. The standard error is indicated after each mean value

Results

Effect of sotalol and practolol on the dose of ouabain and digoxin required to produce rhythm disturbance

A *Digoxin* Pretreatment with sotalol (2 mg per kilogram of body weight) caused a significant increase in the dose of digoxin required to produce PVC VT and VF (Fig 1) Sotalol increased the dose of digoxin required to produce PVC from 161 $\pm$ 8 to 234 $\pm$ 11 μg per kilogram of body weight to produce VT from 172 $\pm$ 6 to 244 $\pm$ 12 μg per kilogram of body weight, and to produce VF from 210 $\pm$ 6 to 282 $\pm$ 10 μg per kilogram of body weight ($p < 0\ 001$) Pretreatment with practolol also produced a significant increase in the dose of digoxin required to cause PVC VT and VF The magnitude of the effect was indistinguishable from that produced by sotalol (Fig 2)

B *Ouabain* The low dose of sotalol (2 mg per kilogram of body weight) did not increase signifi

*Practolol was supplied by th Ay rst Company New York N Y

† Sotalol was supplied by Me d Johns n and Company Evansville, Ind.

*Ouabain was suppl ed by the Eli Lilly Company Indianapolis Ind.

A study of the antiarrhythmic action of certain beta-blocking agents*

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There are several reports which indicate that the antiarrhythmic effect of beta blocking agents is not related to the action of these drugs to block beta adrenergic receptors in the heart. It has been suggested that these agents are effective against digitalis induced arrhythmia because they depress cardiac excitability in a manner similar to that of quinidine[1-4] More recently, however, several investigators have presented evidence which suggests that blockade of beta receptors does play a role in the action of these agents to protect against digitalis induced arrhythmias[5,7] Still others, namely Roberts and co workers[8,9] have developed the concept that the antiarrhythmic effects of beta blocking agents such as pronethalol are related to their depressant action on adrenergic nerves These investigators found that while B TM10, a bretylium like agent which prevents the release of catecholamines from the adrenergic nerve terminals protected against digitalis induced arrythmias, hexamethonium a ganglionic blocking agent, was ineffectual[8,9] These observations, along with the finding that reserpine a catecholamine depleting agent and guanethidine an agent which prevents the release of transmitter from the adrenergic nerve terminals are also effective against digitalis induced arrhythmias,[8,10] suggested that the capacity of an agent to protect against these arrythmias is related, at least in part to an action on adrenergic neurones In this regard Standaert and associates[11] have shown that agents such as pronethalol and propranolol as well as their dextro isomers, are effective in protecting against digitalis induced arrhythmias and have the capacity to produce depression of motor nerve terminals of the cat soleus nerve It is interesting to note that sotalol, a beta blocking agent reported to be ineffective against digitalis induced arrhythmia[4] does not depress motor nerve terminal activity of the cat soleus nerve

Since there is evidence indicating that the antiarrhythmic effects of beta blocking agents may involve an action to depress cardiac excitability a beta receptor blocking action and a neural depressant action it is necessary to determine which of these actions is responsible for the antiarrhythmic effects of a given beta blocking agent in a given experimental setting The present study was performed to examine the effects of MJ 1999 (sotalol) and ICI 50 172 (practolol) on digitalis induced arrhythmias to determine which actions might be responsible for their antiarrhythmic effects Sotalol is a beta blocking agent reported to exert a weak depressant effect on cardiac excitability[12] and on neural activity,[11] whereas practolol is a beta blocking agent which possesses a relatively weak depressant action on cardiac excitability[13] but has the capacity to reduce the cardiac effects of stellate nerve stimulation[14] and depress neural discharges in the adrenergic innervation to the heart[15]

It has been reported that diminution of adrenergic influences to the heart does not uniformly influence the arrhythmogenic capacity of digitalis glycosides[16-18] Erlij and

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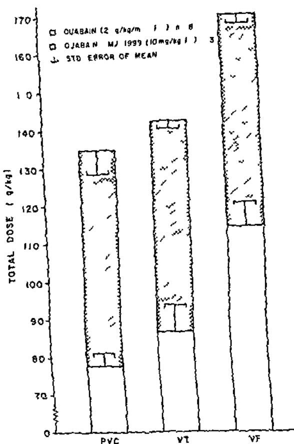


Fig 3 The effect of sotalol on ouabain induced arrhythmias. Sotalol (10 mg per kilogram of body weight) was ad min stered intravenously 15 minutes prior to the start of the ouabain infusion. The dose of ouabain necessary to produce PVC VT and VF is significantly greater in the sotalol treated than in the control group (p < 0 001) See legend to Fig 1 for details

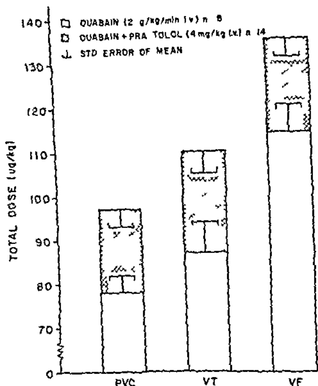


Fig 4 The effect of practolol on ouabain induced arrhythmias Practolol (4 mg per kilogram of body weight) was ad ministered intravenously 15 minutes prior to the start of the ouabain infusion The dose of ouabain at each of the end points is significantly greater in the practolol treated group (p<0 01) See legend to Fig. 1 for details

p > 0 05) In addition sotalol did not affect the maximum rate of VT produced by digoxin (p > 0 05 Table I)

The administration of practolol also produced a significant reduction in heart rate prior to the infusion of digoxin (Table II) Practolol reduced the heart rate from 195 ± 18 to 159 ± 9 b p m a reduction of 36 ± 11 b p m The subsequent infusion of digoxin to these animals caused a further reduction in heart rate of 25 ± 4 b p m prior to the onset of VT which was not significantly different from the 35 ± 8 b p m. reduction in heart rate produced by digoxin in the control series (p>0 05 Table II) Pretreatment with practolol reduced the maximum rate of VT produced by digoxin by 42 b p m (p<0 05 Table II)

It has been suggested that agents which decrease sympathetic activity to the heart increase the cardiotoxic dose of digitalis by reducing heart rate [16,17] Since both sotalol and practolol reduce the heart rate it is possible that their protective action against digitalis is due to this effect. To assess this possibility another agent was used to reduce heart rate namely hexamethonium a ganglionic blocking agent In three animals pretreatment with hexamethonium (2 mg per kilogram of body weight) reduced the heart rate from 217 ± 33 to 153 ± 22 b p m a reduction of 64 ± 12 b p m (p<0 01) Although the decrease in heart rate produced by this agent was greater than that caused by either practolol or sotalol hexamethonium did not increase the dose of digoxin necessary to produce arrhythmia or death (p>0 05) These observations are in accord with those of Ciofalo and associates [9] in which hexamethonium lowered the heart rate to a marked degree but did not influence the time to arrhyth

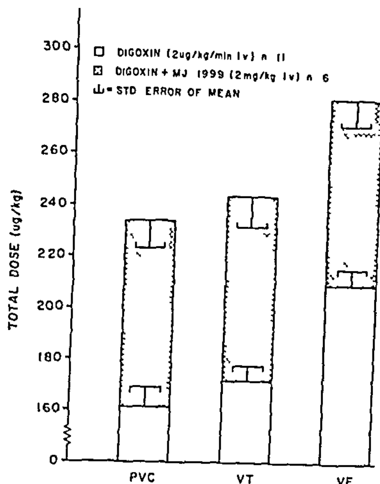


Fig 1 The effect of sotalol on digoxin induced arrhythmias Sotalol (2 mg per kilogram of body weight) was administered intravenously 15 minutes prior to the start of the digoxin infusion The dose of glycoside necessary to produce arrhythmia is indicated on the ordinate The dose of digoxin at each end point is significantly greater in the sotalol treated group ($p < 0.001$) PVC = premature ventricular contraction VT = ventricular tachycardia VF = ventricular fibrillation

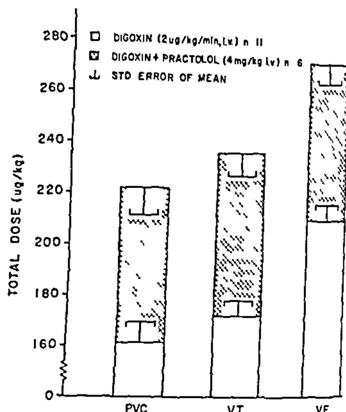


Fig 2 The effect of practolol on digoxin induced arrhythmias. Practolol (4 mg per kilogram of body weight) was administered intravenously 15 minutes prior to the start of the digoxin infusion. The dose of digoxin at each end point is significantly greater in the practolol treated group ($p < 0.001$) See legend to Fig 1 for details.

cantly the cardiotoxic dose of ouabain ($p > 0.05$) However when the dose of sotalol was increased fivefold to 10 mg per kilogram of body weight (high dose), there was significant protection against ouabain induced arrhythmia In this regard the dose of ouabain necessary to produce PVC was increased from 78 ± 4 to 135 ± 6 μg per kilogram of body weight for VT from 87 ± 7 to 142 ± 2 μg per kilogram of body weight and for VF from 114 ± 6 to 169 ± 2 μg per kilogram of body weight ($p < 0.001$, Fig 3)

Pretreatment of the animals with practolol (4 mg per kilogram of body weight) prior to the infusion of ouabain resulted in a significant increase ($p < 0.01$) in the dose of ouabain required to produce PVC VT and VF (Fig 4) Practolol pretreatment increased the dose of ouabain required to produce PVC from 78 ± 4 to 97 ± 4 μg per kilogram of body weight to produce VT from 87 ± 7 to 110 ± 5 μg per kilogram of body weight and to produce VF from 114 ± 6 to 135 ± 4 μg per kilogram of body weight This protective action of practolol against ouabain induced arrhythmia has previously been reported by Papp and Vaughan Williams[13] in the guinea pig

Effect of sotalol and practolol on heart rate changes produced by ouabain and digoxin

A Digoxin. The infusion of digoxin produced a statistically significant decrease in heart rate prior to the onset of ventricular tachycardia in the control animals During the infusion of digoxin the heart rate decreased from 206 ± 9 to 171 ± 10 beats per minute (b p m), a reduction of 35 ± 8 b p m ($p < 0.05$, Table I) Administration of the low dose of sotalol decreased the heart rate from 165 ± 11 to 121 ± 4 b p m (Table I) a reduction of 44 ± 7 b p m ($p < 0.05$) In these animals infusion of digoxin produced a further reduction in heart rate of 21 ± 6 b p m prior to the onset of VT it was not statistically different from the reduction in heart rate produced by digoxin in the control group (35 ± 8 b p m

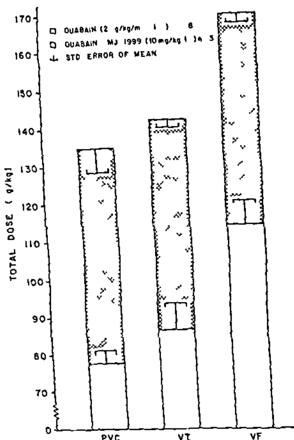


Fig 3 The effect of sotalol on ouabain induced arrhythmias Sotalol (10 mg per kilogram of body weight) was administered intravenously 15 minutes prior to the start of the ouabain infusion. The dose of ouabain necessary to produce PVC VT and VF is significantly greater in the sotalol treated than in the control group (p < 0 001) See legend to Fig 1 for details

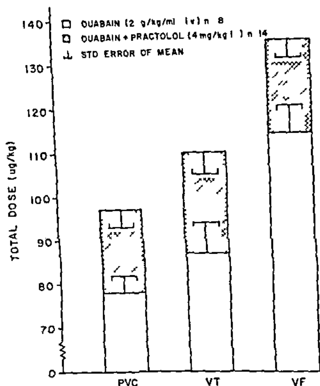


Fig 4 The effect of practolol on ouabain induced arrhythmias Practolol (4 mg per kilogram of body weight) was administered intravenously 15 minutes prior to the start of the ouabain infusion The dose of ouabain at each of the end points is significantly greater in the practolol treated group (p<0 01) See legend to Fig 1 for details

p > 0 05) In addition sotalol did not affect the maximum rate of VT produced by digoxin (p > 0 05 Table I)

The administration of practolol also produced a significant reduction in heart rate prior to the infusion of digoxin (Table II) Practolol reduced the heart rate from 195 ± 18 to 159 ± 9 b p m a reduction of 36 ± 11 b p m The subsequent infusion of digoxin to these animals caused a further reduction in heart rate of 25 ± 4 b p m prior to the onset of VT which was not significantly different from the 35 ± 8 b p m reduction in heart rate produced by digoxin in the control series (p>0 05 Table II) Pretreatment with practolol reduced the maximum rate of VT produced by digoxin by 12 b p m (p<0 05 Table II)

It has been suggested that agents which decrease sympathetic activity to the heart increase the cardiotoxic dose of digitalis by reducing heart rate [16,17] Since both sotalol and practolol reduce the heart rate it is possible that their protective action against digitalis is due to this effect To assess this possibility another agent was used to reduce heart rate namely hexamethonium a ganglionic blocking agent. In three animals pretreatment with hexamethonium (2 mg per kilogram of body weight) reduced the heart rate from 217 ± 33 to 153 ± 22 b p m a reduction of 64 ± 12 b p m. (p<0 01) Although the decrease in heart rate produced by this agent was greater than that caused by either practolol or sotalol hexamethonium did not increase the dose of digoxin necessary to produce arrhythmia or death (p>0 05) These observations are in accord with those of Ciofalo and associates [9] in which hexamethonium lowered the heart rate to a marked degree but did not influence the time to arrhyth

Table I The effect of sotalol on heart rate changes induced by digoxin

	Control (beats/min. ± S.E.) (n=11)	*Sotalol, 2 mg/kg (beats/min. ± S.E.) (n=6)*
Initial heart rate	206 ± 9	165 ± 11
Heart rate after sotalol	–	121 ± 4†
Decrease in heart rate produced by sotalol	–	44 ± 7
Slowest heart rate before ventricular tachycardia	171 ± 10†	102 ± 6*‡
Decrease in heart rate induced by digoxin	35 ± 8	21 ± 6§
Maximum rate of ventricular tachycardia	254 ± 25†	244 ± 4†§

Significantly different from corresponding rate in the control series.
† Significantly different from initial heart rate
‡ Significantly different from heart rate after sotalol.
§ Not significantly different from corresponding rate in the control series.

Table II The effect of practolol on heart rate changes induced by digoxin

	Control (beats/min ± S.E.) (n=11)	*Practolol, 4 mg/kg (beats/min. ± S.E.) (n=6)*
Initial heart rate	206 ± 9	195 ± 18§
Heart rate after practolol	–	159 ± 9†
Decrease in heart rate produced by practolol	–	36 ± 11
Slowest heart rate before ventricular tachycardia	171 ± 10†	134 ± 9 ‡
Decrease in heart rate induced by digoxin	35 ± 8	25 ± 4§
Maximum rate of ventricular tachycardia	254 ± 25†	212 ± 10

Significantly different from corresponding rate in the control series
† Significantly different from initial heart rate
‡ Significantly different from heart rate after practolol
§ Not significantly different from corresponding rate in the control series

mia induced by ouabain Thus it would appear that heart rate changes do not account for the antiarrhythmic action of either sotalol or practolol

B Ouabain The infusion of ouabain in eight control animals reduced the heart rate from 195 ± 7 to 145 ± 9 b p m prior to the onset of VT, a reduction of 50 ± 11 b p m (p<0 05, Table III) In another group of animals prior to the start of the ouabain infusion, the administration of sotalol in the low dose reduced the heart rate from 189 ± 11 to 126 ± 6 b p m, a reduction of 62 ± 9 b p m (p<0 05, Table III) The reduction in heart rate produced by sotalol in this group of animals is approximately 20 b p m greater than the reduction in heart rate produced in the group subsequently infused with digoxin (Table I) The difference in the magnitude of the response to sotalol is probably due to the fact that the initial heart rate in these two groups differed by approximately the same amount i e, 24 b p m After sotalol, the subsequent infusion of ouabain caused a further reduction in heart rate of 30 ± 6 b p m prior to the onset of VT which was not significantly different from the reduction in heart rate produced by ouabain in the control series (p>0 05 Table III) It is important to note that although the low dose of sotalol produced a significant decrease in heart rate it did not afford protection against ouabain cardiotoxicity and did not influence the action of ouabain to reduce heart rate

On the other hand the high dose of sotalol (10 mg per kilogram of body weight) decreased the heart rate by 103 ± 3 b p m a response significantly greater than that observed with the low

Table III The effect of sotalol on heart rate changes induced by ouabain

	(beats/min. ± S.E.) (n=8)	*Sotalol, 2 mg/kg* (beats/min. ± S.E.) (n=7)	*Sotalol, 10 mg/kg* (beats/min. ± S.E.) (n = 3)
Initial heart rate	195 ± 7	189 ± 11§	237 ± 11
Heart rate after sotalol	–	126 ± 6†	133 ± 10†
Decrease in heart rate produced by sotalol	–	62 ± 9	103 ± 3
Slowest heart rate before ventricular tachycardia	145 ± 9†	96 ± 9‡	113 ± 13§
Decrease in heart rate induced by ouabain	50 ± 11	30 ± 6§	20 ± 7
Maximum rate of ventricular tachycardia	256 ± 11†	239 ± 5†§	233 ± 15§

Significantly diff re t from corresponding rate in the control series.
† Signifi antly different from initial heart rate
‡ Significantly d fferent from heart rate after sotalol.
§ Not signific ntly different from corresponding rate in the control series.

Table IV The effect of practolol on heart rate changes induced by ouabain

	Control (beats/min. ± S.E.) (n=8)	*Practolol, 4 mg/kg* (beats/min. ± S.E.) (n=14)
Initial heart rate	195 ± 7	177 ± 7
Heart rate after practolol	–	161 ± 4†
Decrease in heart rate produced by practolol	–	17 ± 3
Slowest heart rate before ventricular tachycardia	145 ± 9†	125 ± 7‡§
Decrease in heart rate induced by ouabain	50 ± 11	36 ± 6§
Maximum rate of ventricular tachycardia	256 ± 11†	227 ± 9

Signifi ntly diffe nt from corresponding ate in the control series.
† Signific ntly diffe ent from nitial heart r te
‡ Significantly different from heart rate after practol l.
§ Not ignificantly diff rent from corresponding rate n the control series.

dose of sotalol ($p < 0.05$ Table III) The reduction in heart rate prior to VT produced by ouabain in the group treated with the high dose of sotalol was not different from the group treated with the low dose of sotalol (20 ± 7 vs 30 ± 7 b p m $p > 0.05$) but it was significantly less than the slowing produced by ouabain in the control group (20 ± 7 vs 50 ± 7 b p m $p < 0.05$) In addition neither the low nor the high dose of sotalol affected the maximum rate of VT produced by ouabain ($p > 0.05$ Table III)

Prior to the infusion of ouabain in 14 animals practolol reduced the heart rate from 177 ± 7 to 161 ± 4 b p m a reduction of 17 ± 3 b p m ($p < 0.05$ Table IV) The difference in magnitude of the reduction in heart rate produced by practolol between this group and that subsequently treated with digoxin (i e 17 vs 36 b p m Table II) is probably due to the fact that the initial heart rate in the two groups differed by approximately the same amount i e about 18 b p m After practolol the infusion of ouabain to the animals produced a reduction in heart rate of 36 ± 6 b p m prior to the onset of VT which was

Table I The effect of sotalol on heart rate changes induced by digoxin

	Control (beats/min. ± S.E.) (n=11)	*Sotalol, 2 mg/kg (beats/min. ± S.E.) (n=6)*
Initial heart rate	206 ± 9	165 ± 11
Heart rate after sotalol	–	121 ± 4†
Decrease in heart rate produced by sotalol	–	44 ± 7
Slowest heart rate before ventricular tachycardia	171 ± 10†	102 ± 6 ‡
Decrease in heart rate induced by digoxin	35 ± 8	21 ± 6§
Maximum rate of ventricular tachycardia	254 ± 25†	244 ± 4†§

Significantly different from corresponding rate in the control series.
† Significantly different from initial heart rate
‡ Significantly different from heart rate after sotalol.
§ Not significantly different from corresponding rate in the control series

Table II The effect of practolol on heart rate changes induced by digoxin

	Control (beats/min ± S.E.) (n=11)	*Practolol 4 mg/kg (beats/min. ± S.E.) (n=6)*
Initial heart rate	206 ± 9	195 ± 18§
Heart rate after practolol	–	159 ± 9†
Decrease in heart rate produced by practolol	–	36 ± 11
Slowest heart rate before ventricular tachycardia	171 ± 10†	134 ± 9 ‡
Decrease in heart rate induced by digoxin	35 ± 8	25 ± 4§
Maximum rate of ventricular tachycardia	254 ± 25†	212 ± 10

Significantly different from corresponding rate in the control series.
† Significantly different from initial heart rate
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B Ouabain The infusion of ouabain in eight control animals reduced the heart rate from 195 ± 7 to 145 ± 9 b p m prior to the onset of VT a reduction of 50 ± 11 b p m (p<0 05, Table III) In another group of animals prior to the start of the ouabain infusion the administration of sotalol in the low dose reduced the heart rate from 189 ± 11 to 126 ± 6 b p m a reduction of 62 ± 9 b p m (p<0 05, Table III) The reduction in heart rate produced by sotalol in this group of animals is approximately 20 b p m greater than the reduction in heart rate produced in the group subsequently infused with digoxin (Table I) The difference in the magnitude of the response to sotalol is probably due to the fact that the initial heart rate in these two groups differed by approximately the same amount i e 24 b p m After sotalol the subsequent infusion of ouabain caused a further reduction in heart rate of 30 ± 6 b p m prior to the onset of VT which was not significantly different from the reduction in heart rate produced by ouabain in the control series (p>0 05, Table III) It is important to note that although the low dose of sotalol produced a significant decrease in heart rate it did not afford protection against ouabain cardiotoxicity and did not influence the action of ouabain to reduce heart rate

On the other hand the high dose of sotalol (10 mg per kilogram of body weight) decreased the heart rate by 103 ± 3 b p m a response significantly greater than that observed with the low

l(−) but not d(+) practolol is effective in protecting against ouabain induced arrhythmia[24] Thus these data suggest that practolol protects against ventricular rhythm disorders produced by ouabain at least in part, by virtue of its capacity to depress adrenergic nervous activity In this regard, it is important to note that sotalol did not depress adrenergic nervous discharge at any dose[27,28] This further indicates that the antiarrhythmic action of the high dose of sotalol is due to a direct action on the heart

It might seem surprising that the small dose of sotalol which is more than sufficient to produce beta receptor blockade did not prevent the effects of increased sympathetic nerve activity on the heart induced by ouabain since the neurotransmitter released in this action norepinephrine produces its effects by beta receptor stimulation However a beta receptor blocking action *per se* might not be sufficient to prevent the cardiac effects of increased adrenergic nervous activity since neural discharge from the adrenergic nerves may be asynchronous and occur at a high frequency and this may readily lead to reversal of the blockade established at the receptor site In this regard it is also possible that the high dose of sotalol was sufficient to produce complete receptor blockade in the presence of ouabain and this action rather than a depressant action on cardiac excitability could explain the antiarrhythmic effect observed in the present study Further experiments are needed to examine this possibility

The results of the present study suggest that there may be a difference in the arrhythmogenic action among the glycosides We have reported previously that in cats pretreated with 6 hydroxydopamine 48 hours prior to the experiment the cardiotoxic dose of ouabain is increased significantly while the dose of digoxin necessary to produce arrhythmia and death is unaffected[29] 6 Hydroxydopamine is an agent that disrupts adrenergic nerve terminals and depletes cardiac but not adrenal medullary catecholamine stores These results suggest that the cardiotoxic action of ouabain but not digoxin is dependent at least in part, on the presence of intact adrenergic innervation in the myocardium However since the arrhythmogenic action of digoxin is decreased by β blockade its cardiotoxicity must be related at least in p[illegible] t[illegible] catecholamines which are liberated from extraneuronal sources The source of the catecholamines may be the adrenal medulla since Dutta and Marks[30] have shown that in the rat there is a striking accumulation of digoxin in the adrenal gland

It is unlikely that the differences in the cardiotoxicity of ouabain and digoxin are due to differences in the curves of action of the glycosides since Levitt and Roberts[18] have reported that the cardiotoxic action of digitoxin which has about the same curve of action as digoxin was reduced by pretreatment with reserpine while digoxin was not affected. In addition our results show that the low dose of sotalol was effective against arrhythmias produced by the glycoside with the slower onset of toxicity (digoxin) digoxin required twice the time to produce arrhythmia than did ouabain At this time interval beta blockade by sotalol should have been considerably less than at the time ouabain induced arrhythmias developed. Consequently if the curve of action of the glycosides was important in explaining the differences in susceptibility to the antiarrhythmic action of the beta blocking agents then the opposite results would be expected, namely that beta blockade would be more effective against ouabain than digoxin induced arrhythmias This was not the case

In many of the investigations concerned with characterizing the antiarrhythmic potential of an agent against digitalis induced arrhythmia the effects of only one glycoside were examined. The results of the present investigation clearly point out the limitations of such an approach since the use of only one glycoside i e ouabain would have led us to the finding that the low dose of sotalol was ineffective in protecting against digitalis induced arrhythmias whereas in fact it was highly effective against digoxin induced arrhythmia

These findings should be of importance in the treatment of digitalis induced cardiotoxicity in a clinical setting since the choice of an antiarrhythmic agent would depend upon the glycoside responsible for the toxicity In addition in patients resistant to the cardiotonic action of digitalis it may be possible to pretreat these persons with an antiarrhythmic agent specific for that glycoside and thus allow higher therapeutic doses of digitalis to be a[illegible]ministered witho[illegible]t concomitant toxicity

similar to the decrease in heart rate produced by ouabain in the control series (p > 0 05) In addition the maximum rate of ventricular tachycardia in the group treated with practolol was significantly lower than that in the control series (p<0 05 Table IV)

Discussion

The mechanism by which beta receptor blocking agents protect against digitalis induced arrhythmias has been the center of controversy It has been suggested that the antiarrhythmic action of this group of agents is related primarily to their action to directly depress cardiac excitability[1,4,21] Indeed a direct effect on the cardiac cell seems to be supported by the observation that in doses reported to be devoid of a significant effect on cardiac excitability[22] sotalol in the present study did not influence ouabain induced ventricular arrhythmias These results confirm the findings of Somani and Lum[4] who have reported previously that sotalol (2 mg per kilogram of body weight) is ineffective in protecting against ouabain induced arrhythmias. On the other hand when we increased the dose of sotalol to that reported to depress cardiac excitability[22] a significant increase in the dose of ouabain necessary to produce arrhythmia and death was observed suggesting that a depressant effect on cardiac excitability may be involved in the protection against ouabain induced arrhythmias produced by this agent

Practolol was effective in increasing the cardiotoxic dose of ouabain even though studies from our laboratory[3] as well as those of Fitzgerald and colleagues[24] and Refsum and Landmark[25] have shown that this agent produces little depression of cardiac excitability In fact Fitzgerald and colleagues[24] have reported that in dogs depleted of catecholamines a depressant effect on the excitability of the cardiac cell does not occur with practolol until a dose of 80 mg per kilogram of body weight has been achieved In this regard we have reported recently that the *d* isomer of practolol is not effective in protecting against ouabain induced arrhythmia while the *l* isomer like the racemate, produces significant protection[26] Lucchesi[2] has reported that both the *d* isomers and racemates of pronethalol and propranolol were equally effective as antiarrhythmic agents and it was suggested that the antiarrhythmic effect is due to a nonspecific depressant action on cardiac excitability by the isomers If practolol produced its antiarrhythmic effects in a manner similar to that suggested for propranolol and pronethalol then both the *d* isomer and the racemate should have protected against the cardiotoxicity of ouabain These data suggest that the capacity to directly depress cardiac excitability is not the only requirement for an agent to protect against digitalis induced arrhythmias Other mechanisms such as beta blockade and depression of adrenergic nervous activity should be considered

The results of the present study indicate that beta receptor blockade may be important as an antiarrhythmic measure but only in specific circumstances. There have been reports by several investigators suggesting that the capacity of an agent to produce beta receptor blockade does indeed contribute to the antiarrhythmic action of these agents against digitalis induced rhythm disorders[5,7] Our results show that both practolol and the low dose of sotalol were effective against digoxin induced arrhythmia Since the capacity to produce beta receptor blockade seems to be the only known action common to these doses of practolol and sotalol it is concluded that a beta receptor blocking action is most likely responsible for the protection against the cardiotoxicity of digoxin This relationship suggests that any agent which can produce beta blockade would protect against digoxin induced arrhythmia

Although the beta receptor blocking action of practolol and sotalol seems to explain their protection against digoxin induced cardiotoxicity whereas an action to depress cardiac excitability seems to explain the protective action of the high dose of sotalol against ouabain induced arrhythmia the effect of practolol to protect against arrhythmias produced by ouabain appears to be mediated through different mechanisms It has been recognized for many years that an important relationship exists between the toxicity of digitalis and the adrenergic nervous system[8,11,15] We have recorded spontaneous discharges from the cardiac accelerator nerves and found that the racemate of practolol reduces adrenergic nervous activity[27] Furthermore we have found that that *l*(−) isomer of practolol but not the *d*(+) isomer is responsible for the action to depress adrenergic nervous activity[28] and that

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Summary

The effects of the beta blocking agents, MJ 1999 (sotalol) and practolol, against ouabain and digoxin induced ventricular rhythm disturbances were studied to evaluate the nature of the action which is involved in the antiarrhythmic action of these beta blocking agents Sotalol and practolol, in doses that have been reported to have little effect on cardiac excitability, protected against digoxin induced arrhythmias Practolol, but not the low dose of sotalol, protected against ouabain induced cardiotoxicity The dose of sotalol necessary to protect against ouabain induced arrhythmia was five times greater than that necessary to protect against digoxin induced arrhythmia and has been reported to directly depress cardiac excitability The maximum rate of ventricular tachycardia produced by ouabain or digoxin was slower in the animals pretreated with practolol but not in those pretreated with sotalol The slowing in heart rate produced by beta blocking agents could not be correlated with the protection afforded against either digoxin or ouabain induced arrhythmia The data suggest that the capacity of beta receptor blocking agents to reduce cardiac excitability may not be the only mechanism responsible for their antiarrhythmic action Both practolol and sotalol protected against digoxin induced arrhythmias and the only action common to both agents is beta blockade Therefore it is suggested that the beta blocking action is responsible for the antiarrhythmic action against digoxin induced arrhythmias However since only practolol protected against ouabain induced rhythm disturbances in doses which do not depress cardiac excitability and since it differs from sotalol in that it has the capacity to depress adrenergic nervous activity in these doses it is suggested that the neural depressant action of practolol is responsible, at least in part, for its antiarrhythmic action against ouabain induced cardiotoxicity

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an area judged to be perfused by the isolated coronary vasculature The sutures were placed in the myocardium in such a manner as to minimize injury to the area immediately underlying the electrode Subendocardial electrograms were recorded by means of Teflon coated stainless steel (7/1 000 inch diameter) hooked electrodes Approximately 1 to 2 mm of the Teflon coating was removed at the angle of the hook The electrodes were introduced into the myocardium through the shaft of a 27 gauge hypodermic needle The needle and electrode were inserted into the myocardium in close proximity to each of the surface electrodes The needle was then slowly withdrawn leaving the electrode in position In this manner surface and deep recordings were paired in each animal with respect to their location within the ischemic zone Electrode depth within the myocardium determined at the end of each experiment averaged 10 2 mm

Three surface and three deep electrograms were recorded simultaneously and continuously during the occlusion period. Precordial lead unipolar potentials were recorded at the high frequency setting using A C amplification and a sensitivity of 2 mv per millimeter No attempt was made to distinguish true S T *segment* elevation from T Q segment depression[15] Systemic blood pressure was monitored from the left femoral artery with a Statham pressure transducer (P 23Db) Heart rate was determined from the R R interval of *the electrograms* In some experiments the heart was paced by means of a Grass stimulator (Model S48) *connected to a* bipolar platinum electrode sutured to the right atrium All parameters were recorded on a multichannel Beckman type R oscillograph at paper speeds of 0 2 and 2 5 cm per second.

After an initial control period of 30 to 45 minutes during which time the injury currents generally subsided to acceptable levels the isolated coronary vasculature was abruptly occluded with a small arterial clamp for a period of 5 minutes Recordings were made at the fast paper speed at one minute intervals during the occlusion The animal was subjected to five intermittent five minute occlusions at exactly 30 minute intervals S T segment voltage elevations from single representative beats were used as an index of the severity of the degree of localized myocardial ischemia Values at each minute interval [illegible] summed (ΣS T) from the respective epicardial and subendocardial recordings and expressed in millivolts as total ΣS T segment deflection Both the total and net (minus control) values were compared Drugs were administered intravenously prior to the fourth occlusion via the cannulated left femoral vein

The following series of experiments were performed

1 To exclude nonspecific effects of the insertion of the intramural electrodes on the epicardial recordings two separate series of control experiments were conducted In the first series of 10 dogs only surface epicardial potentials were recorded in the second control series (eight dogs) both surface and intramural electrograms were recorded Heart rate and blood pressure were allowed to vary

2 Intravenous infusions of isoproterenol (0 25 and 1 μg per kilogram per minute) were evaluated in two separate series of experiments (three and five dogs, respectively) Infusions *were begun* five minutes before and throughout the fourth occlusion period.

3 The effects of intravenous infusions of norepinephrine (0 1 and 1 μg per kilogram per minute) were assessed in five and eight dogs respectively Experimental protocol was similar to that utilized during the isoproterenol studies

4 The effects of pacing and intravenous propranolol were evaluated in seven animals Two control occlusions were performed. Pacing (a mean increase in heart rate of 42 beats per minute) was then instituted two minutes prior to and during the third occlusion Ten minutes after cessation of occlusion and pacing propranolol (1 *mg per kilogram)* was administered intravenously over a five minute period. After 15 minutes a fouth occlusion was performed. During the fifth and final occlusion the heart was again paced, this time at a rate similar to that observed at the end of the second occlusion

In six dogs localized S T segment shifts occurring at variable depths within the left ventricular free wall were assessed during acute coronary occlusion Six Teflon coated stainless steel electrodes (7/1 000 inch diameter) of various *lengths* were embedded in a plexiglass plate (10 by 6 by 1 mm) and were arranged concentrically *(3 mm* diameter) around a small headed platinum electrode (utilized for epicardial recording) The distal tip (0 5 to 1 0 mm) of each stainless steel *electrode* was scraped of its Teflon coating The in

Effects of various agents on regional ischemic myocardial injury Electrocardiographic analysis

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Acute myocardial infarction in man is commonly diagnosed in part, by an analysis of the S T segment displacement in the 12 lead electrocardiogram (ECG) Similarly in the dog heart, acute coronary artery occlusion has been shown to evoke characteristic S T segment shifts in both epicardial[1-3] and intramural[4-6] unipolar ventricular electrograms. This principle has been extended in a recent series of experiments in which the authors utilized the magnitude of the S T segment elevation in multiple epicardial[7,8] subepicardial[9,10] and precordial[11] unipolar electrograms to assess the influence of various physiologic and pharmacologic interventions on the degree and extent of myocardial ischemia during acute coronary artery occlusion

A major consideration of this experimental approach is the degree to which the epicardial, subepicardial and precordial electrograms reflect changes occurring within the deeper regions of the myocardial free wall[6,12] This question becomes particularly relevant in light of the numerous clinical and experimental data documenting an increased susceptibility of the left ventricular subendocardial region to tissue underperfusion and ischemia relative to that of the subepicardial area[13]

The present series of experiments was undertaken (1) to compare the relative magnitude of the S T segment shifts in multiple paired left ventricular epicardial and subendocardial unipolar electrograms during acute coronary artery occlusion, (2) to assess the effects of various interventions on the degree of the S T segment displacement in the subendocardial recordings during the ischemic episode, and finally (3) to compare these changes with those occurring simultaneously in the epicardial electrograms.

Methods

Fifty two healthy male mongrel dogs, weighing between 17 and 23 kilograms were anesthetized with sodium pentobarbital (30 mg per kilogram of body weight, intravenously) intubated, and placed on artificial respiration utilizing room air and a Harvard respiratory pump Anesthesia was maintained with a 5 mg per kilogram per hour pentobarbital infusion A left thoracotomy was performed through the fifth intercostal space and the pericardium was widely incised for maximal exposure of the left side of the myocardium the entire heart was supported in a pericardial cradle No attempt was made to insulate the posterior atrioventricular surface from the underlying pericardium[14] A small branch of the left anterior descending coronary artery supplying the left ventricular free wall generally the second or the third anterior ventricular branch, was carefully dissected and isolated near its origin and a silk tie placed loosely around it. Occasionally either two small anterior ventricular branches of the anterior descending artery or an anterior ventricular branch of the circumflex coronary artery was utilized.

Surface epicardial electrograms were obtained from beaded platinum electrodes (10/1,000 inch diameter) embedded into small plexiglass plates (5 by 5 by 1 mm) The plates were sutured (4 0 silk) directly to the surface of the epicardium in

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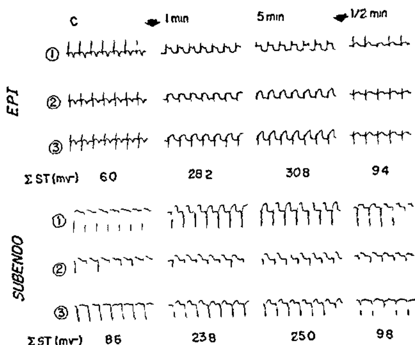


Fig 3 Typical unipolar surface and intramural ventricular electrograms before during and after acute coronary artery occlusion in a pentobarbital anesthetized open chest dog Surface and intramural electrograms were paired with respect to location within the ischemic zone Numbers below each group of tracings refer to the total Σ S T segment displacement from the respective region at each time interval

recordings There was considerable variability in the magnitude of the epicardial S T segment response during the initial coronary artery occlusion five of 46 animals showed minimal or no S T segment displacement at the end of the initial five minute occlusion period. Dye studies in these animals generally revealed a very rapid rate of discoloration of the ischemic zone suggesting a high degree of surface collateral blood flow In contrast three animals exhibiting marked S T segment displacement during occlusion showed slow rates of discoloration in the ischemic zone Data from the former group of animals were not included in this study Surface collateral blood flow thus correlated well with the degree of S T segment shift in the epicardial electrograms

Typical surface recordings from the first control series of experiments before during and after coronary artery occlusion are shown in Fig 1 and the mean Σ S T segment responses at one minute intervals during five intermittent five minute occlusions are depicted in Fig 2 Variable levels of injury current were present in these preocclusion epicardial recordings even after a 30 to 45 minute control period. The magnitude of these injury currents gradually subsided throughout the duration of the experiment Occlusion of the vessel generally produced discernible S T segment displacement within 10 to 30 seconds Both the T and the S waves diminished in amplitude during the ischemic period whereas the R wave decreased, remained unchanged or increased slightly The mean Σ S T segment changes were progressive with the duration of the challenge reaching approximately 80 to 90 per cent of their maximal five minute response after the first two to three minutes of occlusion (Fig 2) Upon release of the occlusion the electrograms exhibited an immediate rapid return to near control configuration (0 to 30 seconds) However in some instances exact preocclusion configurations were not attained for up to one or two minutes after release Subsequent occlusions evoked significantly less total Σ S T segment elevation as compared to the first ischemic challenge ($p < 0.01$) whereas in marked contrast, no significant differences were noted among the total Σ S T segment responses from the second through the fifth occlusions ($p > 0.05$) Similar results were obtained when the responses were compared on the basis of the net (minus preocclu

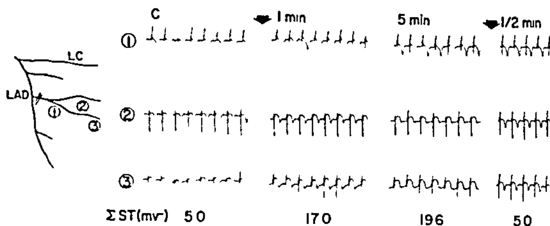


Fig 1 Typical unipolar surface ventricular electrograms before during and after acute coronary artery occlusion in a pentobarbital anesthetized open chest dog Arrows at the top of the figure depict occlusion and release of the vessel Numbers below each group of tracings refer to the sum (Σ) total S T segment displacement at each time interval *LC* left circumflex *LAD* left anterior descending coronary artery

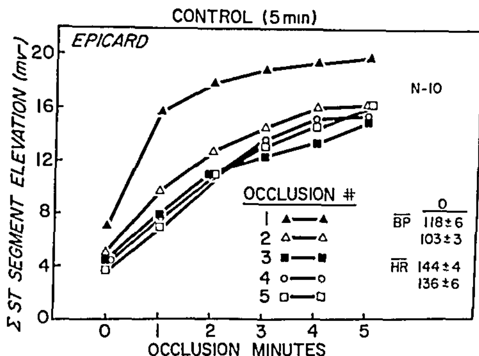


Fig 2 Mean Σ S T segment shifts (elevation) in epicardial ventricular electrograms during five intermittent five minute control occlusion challenges in 10 animals Occlusions were performed at 30 minute intervals. In this and subsequent figures, the maximal ranges in preocclusion mean blood pressure and heart rate for all five occlusions are given

tramural electrodes were inserted into the myocardium and the plate sutured to the myocardial surface Potentials were recorded from depth intervals averaging approximately 2 to 3 mm

Surface myocardial collateral blood flow was estimated in eight dogs by the rapid intravenous injection of 10 ml of a 1 per cent solution of patent blue V dye (Alphazurine Allied Chemical Co) The time required for the occluded area to attain a coloration similar to that of the remaining left ventricular free wall was used as an index of the surface collateral blood flow

Data were analyzed statistically by analysis of variance with the use of a split block design[16] Certain single degree of freedom comparisons were partitioned out of the main effect and the interaction sums of squares Probability values of less than 0 05 were considered significant

Results

Controls Significant site to site variation in the configuration of the surface complexes was noted ranging from the rS to the Rs type of pattern with either large or small inverted T waves. Q waves were not observed in the surface

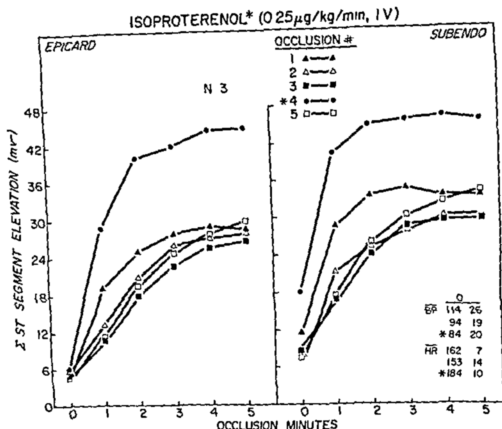


Fig 5 Effects of isoproterenol infused at a dose of 0 25 µg per kilogram per minute on the degree of epicardial and subendocardial mean Σ S T segment shift during acute coronary artery occlusion. Infusion was started five minutes prior to the fourth challenge and continued throughout the duration of the occlusion In this and subsequent figures a closed circle (i e filled) indicates that the regional Σ S T segment responses during drug intervention were significantly different from those of the respective control occlusions. Also shown in this and subsequent figures, in addition to the maximal ranges in mean blood pressure and heart rate during the control occlusions are the mean preocclusion levels of these parameters during pharmacologic intervention.

observed during the second occlusion Although there was variation among animals the intramural total and the net mean Σ S T segment shifts were higher than those of the surface recordings at all times for all five occlusions These differences were significant when calculated for each occlusion over all time intervals (p < 0 01)

Isoproterenol infusion The effects of infusions of isoproterenol (0 25 and 1 µg per kilogram per minute) on the Σ S T segment shifts occurring in the surface and intramural recordings during coronary occlusion are depicted in Figs. 5 and 6 respectively In both series infusions were begun five minutes prior to the fourth occlusion and continued throughout the duration of the ischemic challenge The respective decreases in mean blood pressure from the previous control levels during the low and high dose infusions were 17 and 42 mm Hg heart rate increased by an average of 30 and 57 beats per minute Consistent with the previous control studies were the significant reductions in the total and net Σ S T segment responses from the first to the second occlusion In both experimental series there were no significant differences in the Σ S T segment responses among the second third and fifth occlusions in either the surface or deep recordings (p > 0 05) With the exception of the second occlusion in the low dose series the subendocardial total and net Σ S T segment responses were significantly higher than those of the surface recordings when compared over all minute intervals within occlusions (p < 0 01)

Of particular interest in this experimental series were the isoproterenol induced changes in the level of the control injury currents prior to

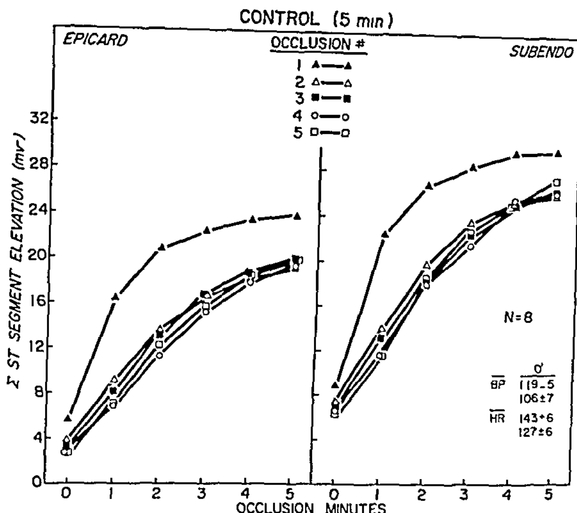


Fig 4 Control epicardial and subendocardial mean Σ S T segment responses to five intermittent five minute occlusion challenges in eight animals Epicardial and subendocardial electrograms were paired with respect to location within the ischemic zone Note the similarity of response in the epicardial tracings in these animals to that of the previous control series (Fig 2)

sion values) Σ S T segment elevations For this reason drug interventions were evaluated during the fourth occlusion with the second, third and fifth occlusions serving as controls Blood pressure and heart rate changes were minimal during the ischemic period Gradual decreases in these parameters did occur however over the duration of the experiment Occasionally some premature ventricular beats were noted, generally at the onset of the initial challenge

Typical tracings and the mean Σ S T segment responses in epicardial and subendocardial electrograms to intermittent coronary occlusion in the second control series are depicted in Figs 3 and 4, respectively Epicardial tracings were essentially similar, both qualitatively and quantitatively to those of the previous control group Insertion of the intramural electrodes therefore would appear to have exerted little if any influence on the quality of the surface recordings

The intramural recordings were invariably of the QS type of pattern Occasionally embryonic R waves were present in these tracings T waves were usually small and inverted During ischemia the intramural S wave amplitude diminished whereas the T wave usually approached isoelectric levels and became upright

The magnitude of the control Σ S T segment elevation in the subendocardial recordings was significantly higher than that in the epicardial tracings ($p < 0.01$) As in the previous series the level of these injury currents gradually subsided with the duration of the experiment Again as in the first control series, the second challenge evoked significantly less total and net Σ S T segment elevations in both the surface ($p < 0.01$) and intramural recordings ($p < 0.01$) as compared to the first occlusion These differences were related largely to decreases in response during the first three minutes of occlusion Subsequent challenges however produced S T segment responses at both recording sites similar to those

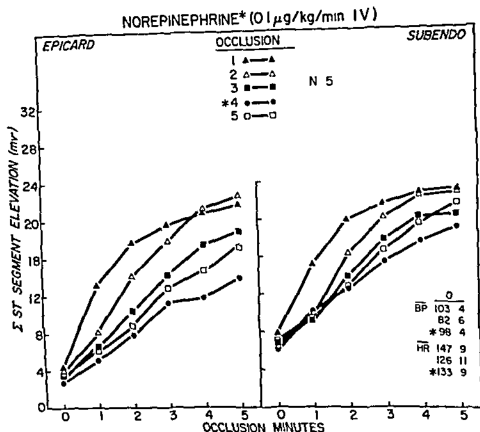


Fig 7 Effects of a 0 1 µg per kilogram per minute infusion of norepinephrine on the degree of epicardial and sub endocardial mean Σ S T segment response during acute coronary artery occlusion For experimental protocol refer to Fig 5

were not observed for occlusions 2 3 and 5 at the low dose ($p > 0.05$)

As in the isoproterenol series the intramural recordings exhibited marked increases in the level of control injury current at the high doses whereas the surface recordings showed only slight increases Similar increases in injury current prior to occlusion were not observed during the low dose infusion Of particular interest were the contrasting Σ S T segment responses to the low and high dose infusions of norepinephrine during coronary occlusion Whereas the low dose significantly reduced the total Σ S T segment elevation during occlusion at both recording sites (Fig 7 $p < 0.05$) the high dose produced significant increases in these parameters ($p < 0.01$) In the latter series, the maximal increases in the mean total Σ S T segment responses above those of the control challenges occurred within the first two minutes of occlusion in both the surface and intramural recordings Somewhat greater reductions in the level of ischemic response were noted in the surface recordings during the low dose infusion Regional differences were not apparent at the high dose however

Pacing and propranolol Epicardial and subendocardial mean Σ S T segment responses to intermittent coronary occlusion during right atrial pacing (third occlusion) and 1 mg per kilogram of propranolol (fourth occlusion) are illustrated in Fig 9 During the fifth occlusion the heart was paced at a rate similar to that present at the end of the second occlusion The initial occlusion time response curves for both the surface and intramural recordings differed somewhat from those of the initial control series Specifically although there was a significant diminution in the mean total Σ S T segment elevation from the first to the second challenge at both regions ($p < 0.01$) these reductions were somewhat less than those observed previously In addition these differences were not significant when based

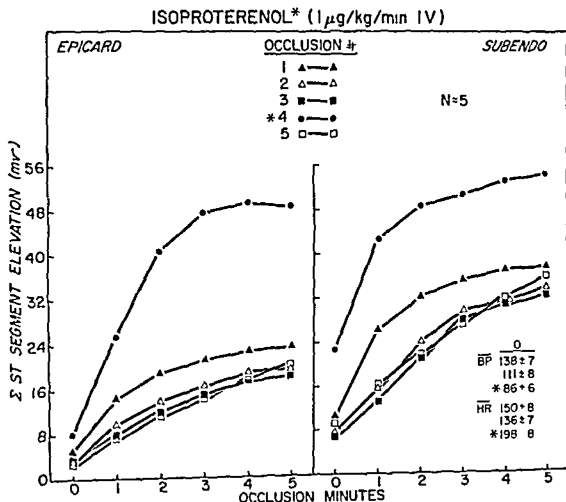


Fig 6 Effects of a 1 μg per kilogram per minute infusion of isoproterenol on the degree of epicardial and subendocardial Σ S T segment response during acute coronary artery occlusion Experimental protocol similar to that for Fig 5

coronary artery occlusion At both dose levels significantly greater increases in the level of intramyocardial injury current occurred as compared to those of the epicardial recordings (p < 0 01) During the ischemic challenge both doses of isoproterenol significantly increased the epicardial and subendocardial total and net Σ S T segment responses above those of control occlusions 2, 3, and 5 (p < 0 01) The magnitude of these responses appeared to increase with the dose Also at the high dose the surface recordings exhibited somewhat greater responses during infusion as compared to the intramural recordings

Norepinephrine infusion Norepinephrine was infused intravenously over 10 minutes at doses of 0 1 and 1 μg per kilogram per minute in five and eight dogs respectively In both groups the experimental protocol was similar to that of the isoproterenol series During the low and high dose infusions, blood pressure increased above the previous control levels by an average of 10 and 82 mm Hg respectively Heart rate decreased slightly at both dose levels

Figs 7 and 8 illustrate the respective mean responses in the Σ S T segment shifts in the epicardial and subendocardial recordings during the low and high dose infusions Responses to the first three control occlusions in the latter series generally resembled those of the previous control experimental series whereas in the low dose series the reduction in mean Σ S T segment elevation from occlusion 2 to occlusion 3 equalled or exceeded that which occurred between the first two occlusions In both series the subendocardial total Σ S T segment shifts were significantly higher than those of the surface electrograms during each occlusion when calculated over all minute intervals within the occlusion (p < 0 01) Similar differences were not apparent, however for the net Σ S T segment responses. When compared on this basis site differences

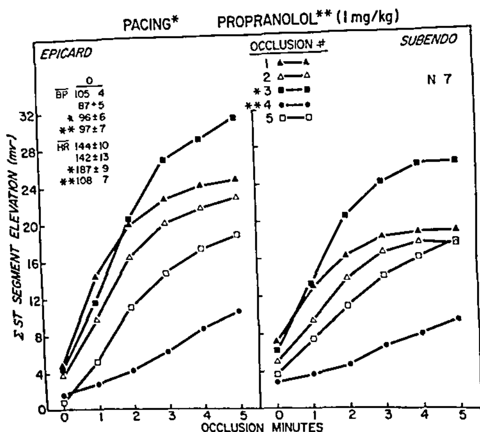


Fig 9 Effects of increasing heart rate and intravenous propranolol on the degree of regional ischemic Σ S T segment response during acute coronary artery occlusion Pacing (+42 beats per minute) was instituted two minutes prior to and throughout the third occlusion (■) Propranolol was administered prior to the fourth occlusion (●) During the fifth and final challenge the heart was again repaced at a rate similar to that of the prepropranolol level (□)

T segment shifts during acute coronary artery occlusion (see Methods)

Two of these six animals exhibited greater subendocardial S T segment displacement during coronary artery occlusion Typical tracings from one such experiment are illustrated in Fig 10 The remaining four animals showed marked regional variations in the degree of S T segment displacement during occlusion (Fig 11) These findings support our previous data and suggest the occurrence of more heterogeneous intramyocardial ischemia during acute coronary artery occlusion To test whether injury currents could be elicited in such a highly localized manner intramural electrodes were inserted under nonischemic control conditions immediately adjacent to the electrode plaque In all instances marked injury currents appeared in this electrode with no apparent effect on the other recordings (Fig 11)

Discussion

Experimental studies have demonstrated that the normal epicardial to endocardial flow distribution ratio is altered favorably toward the epicardium during partial[17] and total[18] coronary artery occlusion Metabolic studies[19,20] also support the hypothesis that the subendocardium is more vulnerable to ischemia as compared to the subepicardial regions Clinically subendocardial necrosis has been documented in patients with little or no apparent coronary pathology[21] It is postulated that the subendocardium is more vulnerable to tissue ischemia as a result of a normal gradient in systolic coronary blood flow coupled with the inability of the subendocardial vasculature to undergo adequate compensatory dilation during diastole under conditions of a reduced coronary blood supply[13] Hence pharmacologic intervention under ischemic conditions might evoke complex interactions between

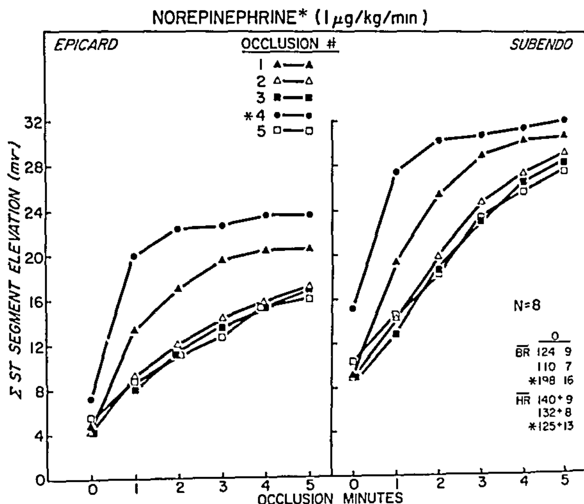


Fig 8 Effects of norepinephrine infused intravenously at a dose of 1 0 µg per kilogram per minute on the degree of epicardial and subendocardial mean Σ S T segment shift during acute coronary artery occlusion For experimental protocol refer to Fig 5

on net Σ S T segment responses (p> 0 05) Also during the first two occlusions the epicardial mean total and the net Σ S T segment changes were significantly higher than those recorded from within the myocardium (p < 0 01) During the fifth occlusion however these regional differences were not statistically significant (p > 0 05)

As shown in Fig 9 elevating the heart rate by an average of 42 beats per minute significantly increased the epicardial and subendocardial mean total and net Σ S T segment responses above those of the second occlusion (p < 0 01) During the first 2 minutes the intramural tracings exhibited a somewhat greater magnitude of increase above the second occlusion as compared to the surface recordings After 3 minutes however these differences were no longer apparent

In contrast to pacing intravenous propranolol significantly lowered the mean total and net Σ S T segment elevations during coronary occlusion as compared to those observed during the second occlusion (p < 0 01) Significant reductions were observed at all minute intervals during this five minute challenge Propranolol appeared to evoke a somewhat greater reduction in the degree of ischemic response in the epicardial recordings as compared to the intramural electrograms Re elevating the heart rate to the pre propranolol control level resulted in essentially similar control net Σ S T segment responses in the epicardial and subendocardial recordings (occlusion 5 Fig 9)

Variable depth electrograms The amplitude of the regional intramural S T segment displacement during coronary artery occlusion has been reported to increase progressively from an inner to outer direction [5] Our findings however suggest a greater variability in the degree of ischemic S T segment displacement in different regions of the left ventricular free wall These apparent differences prompted a series of experiments in which a somewhat different approach was taken to record variable depth intramural S

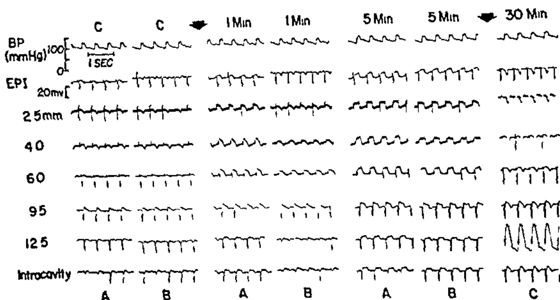


Fig 11 Typical unipolar epicardial and intramural ventricular electrograms before during (one and five minutes) and after acute coronary artery occlusion in a pentobarbital anesthetized open chest dog Intramural electrograms were recorded at progressively deeper levels (2 to 4 mm) from within the left ventricular free wall during two five minute occlusions *(A* and *B)* at an interval of 30 minutes In this particular animal the maximal S T segment displacement during the initial occlusion (A) occurred at electrodes lying 4 and 6 mm within the myocardium Somewhat less S T segment shift was noted at all sites after one minute of the second occlusion *(B)* After five minutes however the magnitude of the S T segment displacement of occlusion *B* more closely approximated that of occlusion *A* Blood pressure and heart rate were essentially unchanged between these challenges. *Panel C* illustrates the effects of inserting a plunge electrode (11 mm) immediately adjacent to the recording area Marked localized injury current appeared in this recording with little or no change in the configuration of other electrograms

phosphokinase (CPK) enzyme depletion 24 hours after occlusion with 15 minute postocclusion epicardial S T segment elevation tend to indirectly support this hypothesis [12] These workers reported no epicardial S T segment depression from areas overlying subendocardial regions exhibiting up to 50 per cent reduction in CPK levels 24 hours after occlusion

In the present experimental series ischemia was produced throughout the entire thickness of the myocardial wall (transmural infarction) Thus accordingly electrodes placed within this ischemic region always demonstrated S T segment elevation The question still remains however whether these shifts reflect primarily localized tissue injury or whether they reflect net potential differences from within the entire myocardial wall The present ECG data with the plunge intramural electrode clearly demonstrate that highly localized injury currents can be evoked within the left ventricular free wall (Fig 11) Kennamer and associates[4] reported that injury currents recorded from plunge intramural electrodes were influenced little by injury to nearby cardiac tissue Sayen and co workers[6] also noted a poor correlation between epicardial S T segment shifts and simultaneous intramyocardial electrical activity particularly in areas of limited infarct size Our findings also suggest a certain degree of independency between epicardial and subendocardial electrical activity as evidenced by (1) the relatively larger dose related increases in the level of the control subendocardial injury current during isoproterenol infusion and (2) marked regional differences in the degree of intramural S T segment shifts during coronary occlusion (Fig 11) Accordingly then the present ECG data were tentatively interpreted as reflecting primarily localized tissue ischemia [4,12,29]

Confusion also exists regarding the relative magnitudes of the epicardial and subendocardial S T segment displacements during acute coronary artery occlusion Rakita and colleagues[5] reported an increasing ischemic S T segment displacement from endocardium to epicardium.

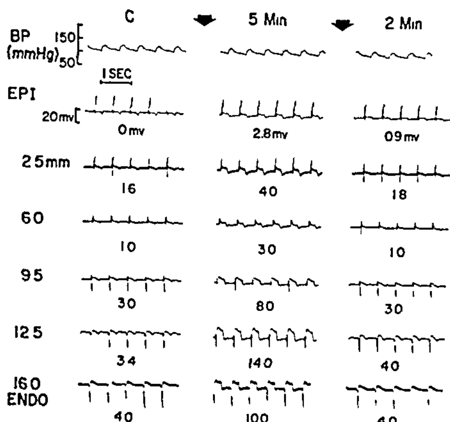


Fig 10 Typical unipolar epicardial and intramural ventricular electrograms before during (five minutes) and after acute coronary artery occlusion in a pentobarbital anesthetized open chest dog Intramural tracings were recorded at progressively deeper levels (3 to 4 mm intervals) from within the left ventricular free wall Note the respective progressive increase and decrease in R wave and S wave amplitude from endocardium to epicardium in the control panel Notching or slurring of the S wave (R wave potential) was observed at the 12 5 and 16 0 mm electrodes Total wall thickness was 20 mm After five minutes of occlusion greater S T segment displacement occurred at electrodes lying within the deeper regions of the myocardium All recordings exhibited essentially normal configuration two minutes after release of the occlusion

myocardial oxygen delivery and demand at different regions within the left ventricular free wall The present study attempts to explore this possibility by comparing the effects of various agents on the magnitude of the S T segment shifts in multiple epicardial and subendocardial electrograms during acute coronary artery occlu sion

As noted previously [7,22] the degree of epicardial S T segment displacement has been correlated with the degree of change in coronary blood flow,[2] membrane potential [23] and anaerobic tissue metabolism [12] Presumably therefore, in the acute setting, ECG S T segment displacement directly reflects the level of myocardial cellular injury ECG comparison of regional tissue ischemia, however still requires consideration of (1) the localized nature of the responses and (2) the degree of regional S T segment displacement during occlusion alone

Early studies by Wolferth and associates[3] and Hellerstein and Katz[1] demonstrated consistent S T segment changes in electrodes remote from the site of injury The latter workers concluded that the direction of the S T displacement is depen dent purely on the spatial orientation of the ex ploring electrode in relation to the theoretical surface between injured and uninjured areas of the myocardium Thus in their study negative epicardial S T segment displacement was noted with underlying subendocardial injury while subepicardial injury evoked S T segment depres sion in left ventricular intracavity potentials. Subsequent experimental studies however failed to demonstrate consistent S T segment de pression in epicardial leads overlying areas of documented subendocardial injury[12] and infarc tion [24,26] These studies and others[27] led some of these workers to postulate that epicardial S T segment depression occurs as a primary event as sociated with a milder degree of subepicardial ischemia[28] as opposed to the reciprocal theory proposed by Hellerstein and Katz [1] Recent studies correlating regional myocardial creatine

level of ischemic S T segment displacement in epicardial[7] and precordial[11] recordings in the occluded canine heart Our findings also demonstrate significant reductions in ischemic S T segment displacement in both epicardial and subendocardial recordings after propranolol As with the previous interventions significant regional differences in the *magnitude of these reductions* were not apparent after administration of this agent The present ECG data therefore do not reflect the previously reported favorable redistribution of myocardial blood flow to the deeper regions of the occluded canine myocardium [18,35]

Maroko and colleagues[7] demonstrated marked reductions in the level of the ischemic response in two animals whose heart rates were maintained constant after β adrenergic receptor blockade with propranolol Pelides and associates[2] also reported a lack of correlation between heart rate and degree of reduction in precordial S T segment elevation after practolol in patients suffering acute myocardial infarction Our findings suggest however that propranolol decreased the degree of ischemic S T segment response largely by slowing the rate of contracture

Results of the present investigation suggest the following

1 Marked variability in the level of epicardial and intramural ischemic S T segment shifts during acute coronary artery occlusion Equal or greater subendocardial S T segment elevation was observed in 58 per cent of the animals during the initial five minute occlusion challenge

2 Drug induced regional differences in the degree of ischemic S T segment response as demonstrated by the effects of isoproterenol and norepinephrine in the absence of coronary artery occlusion

3 Increases in the level of the epicardial and subendocardial ischemic responses with increasing heart rate intravenous isoproterenol (0 25 and 1 0 μg per kilogram per minute) and norepinephrine (1 0 μg per kilogram per minute) and decreases with norepinephrine (0 1 μg per kilogram per minute) and propranolol (1 mg per kilogram)

4 Similar qualitative and quantitative responses in the ischemic S T segment displacement in epicardial and subendocardial recordings with the above interventions

Summary

Myocardial unipolar electrical potentials were recorded in 52 open chest dogs from multiple epicardial and subendocardial sites in an area judged to be perfused by a small branch of the anterior descending coronary artery The degree of individual electrode S T segment shift was utilized as a measurement of the degree of localized myocardial ischemia Individual electrode voltage shifts were summed (Σ) from the respective recording areas and expressed in millivolts as total epicardial and subendocardial Σ S T segment elevation Repeated five minute occlusion challenges at 30 minute intervals resulted in reproducible degrees of Σ S T segment shifts at both sites after the second occlusion challenge Isoproterenol (0 25 and 1 0 μg per kilogram per minute) and norepinephrine (1 0 μg per kilogram per minute) infused intravenously increased the degree of the Σ S T segment response during the ischemic challenge as did increasing the heart rate an average of 42 beats per minute

Conversely norepinephrine (0 1 μg per kilogram per minute) and propranolol (1 mg per kilogram) reduced the degree of ischemic Σ S T segment response Consistent regional differences in either the direction or magnitude of the ischemic Σ S T segment shifts were not observed during any of the above interventions It is concluded that changes in the epicardial electrograms largely reflect the degree of subendocardial ischemia as determined electrocardiographically under the above experimental conditions

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These data would appear to conflict with the current hypothesis regarding an increased vulnerability of the deeper regions of the left ventricular free wall to tissue hypoxia Our findings, however, indicate an equal or greater degree of subendocardial S T segment displacement during the initial challenge in 21 of 36 (58 per cent) of the animals Although electrode placement may have partially accounted for this finding (broader subendocardial ischemia)[5], this does not appear to be the entire explanation since essentially similar results were noted in our variable depth electrode experiments Durrer and co workers[30] also reported greater heterogeneity in the degree of intramural S T segment shift during coronary artery occlusion in the canine heart.

The consistent reduction in the level of the S T segment displacement from the first to the second occlusion is difficult to explain Although a slight increase in collateral blood flow could account for this finding this does not appear to be a likely explanation [31] Also since blood pressure and heart rate decreased progressively with the duration of the experiment, it is equally unlikely that this early response was related entirely to a reduction in myocardial oxygen requirement Previous studies failed to note any significant reduction in the level of the ΣS T segment response between control challenges after 5 10 and 15 minutes of occlusion [7,11] In the present experiments the reduction in response was always maximal after the first minute of occlusion and decreased progressively with the duration of the challenge (Fig 11) Conceivably therefore similar differences in the level of ischemic response may not have appeared at later intervals

The degree of epicardial S T segment shift during coronary occlusion was significantly increased during right atrial pacing and intravenous infusion of isoproterenol whereas propranolol had an opposite effect Norepinephrine infused intravenously produced variable results depending on the dose a dose of 0 1 μg per kilogram per minute tended to decrease the degree of epicardial S T segment displacement whereas a high dose (1 0 μg per kilogram per minute) clearly increased the response In all instances subendocardial S T segment displacement generally paralleled that of the epicardial electrograms

Previous studies have demonstrated a general inverse relationship between systemic blood pressure and the degree of epicardial S T segment shift during coronary artery occlusion [7,9,11] The present dose dependent findings with norepinephrine however, suggest that high doses of this catecholamine can evoke significant increases in the degree of ischemic S T segment response during coronary artery occlusion Since similar pressor responses evoked by methoxamine[7] and phenylephrine[10] resulted in reductions in the degree of S T segment elevation during occlusion a direct myocardial effect of norepinephrine appears to be involved.[3] Similar paradoxical myocardial effects with infusions of norepinephrine have been described in animals subjected to diffuse coronary embolism with plastic microspheres [33] ECG evidence is thus presented supporting previous metabolic data suggesting a deleterious myocardial effect with high dose infusions of norepinephrine in patients with acute myocardial infarction In our studies regional differences in the degree of ischemic response were not observed at either dose level of norepinephrine This is somewhat surprising since an elevated left ventricular systolic pressure would be expected to increase the gradient in systolic coronary blood flow and result in a greater subendocardial S T segment elevation as compared to the epicardial recordings

Isoproterenol also failed to produce consistent regional differences in the level of S T segment displacement during coronary artery occlusion Marked dose related regional differences were noted however during isoproterenol infusion in the absence of coronary artery occlusion These data support recent observations suggesting a relative underperfusion of the left ventricular subendocardial region in the normal canine heart during isoproterenol infusion [34] The above results however are at variance with the metabolic data reported recently by Griggs and co workers[19] in which no significant variation in epicardial and subendocardial metabolism was noted during a 10 μg per minute infusion of isoproterenol Under conditions of a partially compromised coronary circulation however isoproterenol evoked greater increases in the lactate/pyruvate ratio in the subendocardium relative to that of the subepicardial region

Propranolol has been shown to decrease the

Subendocardial underperfusion during acute aorticopulmonary shunting in anesthetized dogs

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Surgical creation of aorticopulmonary (A P) shunts is commonly performed to increase pulmonary blood flow in patients with cyanotic congenital heart disease Unfortunately heart failure not infrequently occurs in the postoperative period which generally has been thought to be due to volume overloading of the left heart. Diacoff[1] found that the mean aortic pressure drop measured at the time of operation was useful in predicting when an A P shunt was too large and would lead to heart failure Thus it is possible that A P shunts stress the heart in two ways (1) by increasing the volume load of the left heart and (2) by reducing aortic pressure and decreasing coronary perfusion Although the clinical effects of excessive shunt volume are well known the effects of A P shunting on coronary hemodynamics have received little attention

Coronary perfusion of the left ventricle is determined by the coronary driving pressure and coronary vascular resistance Coronary driving pressure itself is determined by the aortic perfusion pressure and the opposing intramyocardial pressure[2] In the subepicardial region the intramyocardial pressure is small and offers little opposition to systolic perfusion whereas in the subendocardial region the intramyocardial pressure approximates aortic systolic pressure and may nearly completely impede systolic coronary perfusion[3,6] This means that although coronary flow to the deeper layers of the left ventricle is affected by changes in mean aortic pressure it is mainly dependent upon maintenance of aortic diastolic pressure (Fig 1) Previous studies have shown that with A P shunting aortic diastolic pressure falls[7,8] The fall in aortic diastolic pressure lowers coronary driving pressure to the subendocardium Initially the decrease in coronary driving pressure may be compensated for by coronary vasodilatation but when the coronary vessels become maximally vasodilated, a further decrease in aortic diastolic pressure would reduce coronary flow To determine if coronary insufficiency does occur we studied the effects of acute A P shunts on regional coronary hemodynamics

Methods

We anesthetized seven dogs weighing between 18 and 30 kilograms with sodium pentobarbital 30 mg per kilogram intravenously The dogs were ventilated by a Harvard respirator with oxygen enriched gas mixtures to give arterial oxygen tensions greater than 100 mm Hg and carbon dioxide tensions between 28 and 36 mm Hg A bilateral thoracotomy was performed through the fourth intercostal space Catheters were placed into both femoral arteries a femoral vein right internal mammary artery left atrium a distal pulmonary artery and directly into the body of the right ventricle Pressures were measured with Statham P23DB transducers and recorded by a Beckman oscillograph A segment of proximal descending aorta was dissected, clamped and transected Aortic flow was re established by introducing 2 No 34 Bardex tubes into the proximal and distal aortic segments and attaching them to a Y connector The third arm

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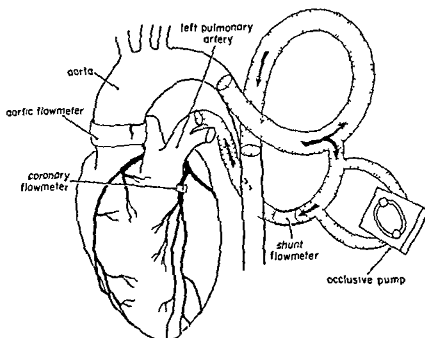


Fig 2 Diagram showing experimental preparation. Direct A P shunt route is via aortic cannula to superior branch of left pulmonary artery Indirect A P shunt route is via aortic cannula to occlusive pump then to the left pulmonary artery

Table I Hemodynamic findings at time of myocardial flow determinations

	Control (M ± 1 S.D)	*A P shunt (direct)* (M + 1 S D)	*A P shunt (indirect)* (M ± 1 S.D)
Heart rate (beats/min.)	116 ± 21 4	129 ± 18 7	115 ± 20 8
Left ventricular output (L/min.)	1 3 ± 0 24	2 9 ± 0 46	2 9 ± 0 49
Stroke volume (ml)	11 4 ± 1 3	22 8 ± 4 0	25 2 ± 4 3
Shunt flow (L/min.)	– –	2 4 ± 0 49	2 4 ± 0 43
Right ventricular systolic pressure (mm Hg)	26 4 ± 6 7	֊2 0 ± 5 1	33 0 ± 6 4
Left atrial mean pressure (mm Hg)	9 3 ± 3 2	12 3 ± 6 2	11 8 ± 4 4
Aortic pressure (mm Hg) systolic	119 ± 20 1	117 ± 19 4	137 ± 15 4
diastolic	68 3 ± 18 2	25 0 ± 6 2†	55 7 ± 22 5

p < 0 05 (difference from control)
†p < 0 05 (difference between shunt groups)

tissue from each region was placed in one or more vials weighed and counted in a well scintillation counter The radioactivity emitted by each nuclide was determined by a modification of the method of Rudolph and Heymann[14]

Results

The hemodynamic findings at the time of myocardial flow determinations are shown in Table I Heart rate increased during A P shunting Left ventricular output increased by an average 125 per cent from control values with both types of shunts Right ventricular left atrial and aortic systolic pressures did not significantly change from control Aortic diastolic pressure fell significantly with direct A P shunts but it did not significantly differ from control values with indirect A P shunts

Absolute regional coronary flow values are shown in Table II Total coronary flow to the left

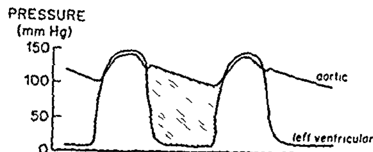


Fig 1 Graphic representation of phasic changes in coronary driving pressure within the subendocardial region of the left ventricle Note during systole left ventricular pressure obliterates the driving pressure as a result coronary driving pressure to the subendocardium is diastolic (hatched area)

of the Y was connected to a No 24 Bardex tube with a cannulating electromagnetic flow transducer (Statham Model SP 2202) in line This cannula was inserted into the superior branch of the left pulmonary artery facing proximally The latter conduit represented the efferent limb of the A P shunt Flow could be diverted to the left pulmonary artery by either of two routes shown in Fig 2 (1) directly to the left pulmonary artery (direct A P shunt) or (2) indirectly by way of an occlusive roller pump (indirect A P shunt) The volume of flow through the direct A P shunt was controlled with a screw clamp flow through the indirect A P shunt was controlled by regulating the speed of the roller pump Cardiac output was recorded with a cuff electromagnetic flow transducer (Statham Model SP 2202) around the ascending aorta Shunt flow was measured with the cannulating electromagnetic flow transducer At the end of each study the flow transducers were calibrated with timed volume collections of the animal s blood A 2 0 mm diameter electromagnetic flow transducer was placed around the proximal portion of the left anterior descending coronary artery Zero flow reference levels were determined by 8 sec occlusions of the left anterior descending coronary artery distal to the flow probe The flow debt incurred during occlusion was calculated as the baseline flow times the duration of occlusion The payback of this debt was calculated by planimetry of the area beneath the mean coronary flow curve and above the base line flow level from the time of release of the occlusion until mean coronary flow stabilized at the preocclusion level The ratio of this area to the flow debt area was multiplied by 100 to give the per cent hyperemic response 100 per cent indicates that flow debt was exactly repaid[9]

The oxygen demand of the left ventricle was estimated from its tension time index (TTI) measured by planimetry of the area beneath the systolic portion of the aortic pressure tracing as described by Sarnoff and associates[10] All TTIs were expressed as mm Hg sec/min The coronary driving pressure of the left ventricular subendocardial region was estimated by planimetry of the area between the aortic diastolic pressure and the mean left atrial pressure tracings This area per minute is referred to as the diastolic pressure time index DPTI (Fig 1)[11]

We measured regional coronary blood flow by injecting differently labeled batches of radioactive microspheres into the left atrium as described previously[12,13] These particles are mixed with the blood in the heart and are distributed within the myocardium in proportion to regional blood flow The spheres are trapped in the myocardium and have negligible recirculation Only microspheres with mean diameter of 7μ (range 4 to 12) with ^{141}Ce ^{85}Sr, and ^{46}Sc were used Regional myocardial flow was determined from the equation myocardial flow/myocardial nuclide activity equals reference sample flow reference sample nuclide activity Reference blood samples were collected from each femoral artery at the onset of the microsphere injection and for a total period of 90 sec

Three myocardial flow determinations were made in each animal (1) during a stable control state (2) during direct A P shunting, and (3) during indirect A P shunting The magnitude of the latter shunt was adjusted to make shunt flow equal to that of the direct A P shunt. Left ventricular output was kept constant during A P shunting by infusion of fresh whole blood.

Coronary vascular resistance was calculated according to the general equation resistance equals pressure drop across the vascular bed divided by flow In the specific case of the left ventricular subendocardial region coronary vascular resistance was estimated by dividing the mean diastolic pressure (distolic pressure time index) by subendocardial coronary flow

At the end of the experiment the dog was killed and the heart removed The atria valves great arteries large coronary vessels, and epicardial fat were removed from the ventricles The free walls of the right and left ventricles were cut from the ventricular septum and divided into subendocardial middle and subepicardial layers of about equal thickness. The ventricular septum was divided into right middle and left layers the

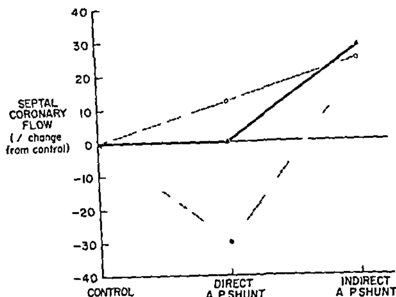


Fig 4 Changes in regional septal coronary flow with A P shunting Asterisk indicates significant difference ($p < 0.05$) between adjacent points — — Δ — — = changes in total septal flow • = changes in flow to left side of septum ○ = changes in flow to right side of septum

creased 25 per cent The distribution of coronary flow throughout the free wall of the right ventri cle did not change significantly Changes in coro nary flow to the left side of the ventricular sep tum resembled those in the subendocardial region of the left ventricular free wall that is flow to this area decreased approximately 30 per cent with direct A P shunts but increased ap proximately 21 per cent with indirect A P shunts (Fig 4)

Coronary hemodynamics in the subendocar dial region of the left ventricular free wall differed significantly between the two types of shunts (Fig 5) With direct A P shunts coronary driving pressure in this region fell approximately 60 per cent whereas when aortic diastolic pressure was maintained with the indirect shunts coronary driving pressure returned to control values The estimated coronary vascular resistance in the left ventricular subendocardial region fell approximately 34 per cent with direct shunts and 20 per cent with indirect shunts In the former group the fall in coronary vascular resistance was accounted for by the decrease in coronary driving pressure In the indirect shunt group the fall in coronary vascular resistance was secondary to an increase in coronary flow since coronary driving pressure did not differ from control Post ischemic reactive hyperemic responses were measured in the three states to estimate changes in coronary vasomotor reserve These responses were abnormal with the direct A P shunts in that coronary flow payback aver aged only 84 per cent of the flow debt With in direct A P shunts coronary flow payback aver aged 156 per cent of the flow debt indicating a significant increase in coronary vasomotor reserve With indirect A P shunts an increase in the left ventricular TTI was accompanied by an increase in coronary flow throughout the entire free wall of the left ventricle In contrast, with direct A P shunts the TTI did not significantly change but was accompanied by a fall in suben docardial flow suggesting that coronary perfu sion did not keep pace with the myocardial oxy gen needs

To determine if we could predict when the subendocardial vessels were unable to maintain coronary flow we related the coronary DPTI to the TTI The DPTI reflects the driving pressure aspect of myocardial oxygen supply while the TTI reflects the pressure aspect of the myocardial ox ygen demand The ratio of DPTI/TTI was used to estimate the balance between supply and de mand The ratio of DPTI/TTI fell from an aver age of 1 05 ± 0 13 (S E) in the control sta e to

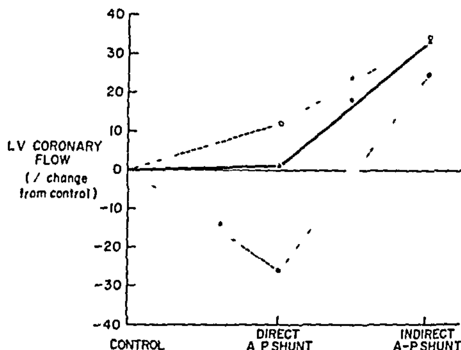


Fig 3 Changes in regional left ventricular coronary flow with A P shunting Asterisk indicates significant difference (p < 0 05) between adjacent points — — Δ — — = changes in total left ventricular flow • = changes in subendocardial flow O = changes in subepicardial flow

Table II Regional myocardial flows (in ml /100 Gm /min)

	Control (M ± 1 SD)	Direct A P shunts (M ± 1 SD)	Indirect A P shunts (M ± 1 SD)
Right ventricular	43 ± 16	45 ± 12	46 ± 8 0
Subendocardial	37 ± 14	45 ± 13	45 ± 8 1
Middle	40 ± 17	47 ± 14	44 ± 7 9
Subepicardial	48 ± 18	42 ± 11	50 ± 13 0
Septal	72 ± 21	72 ± 26	93 ± 17 †
Right layer	65 ± 14	72 ± 21	79 ± 12
Middle layer	77 ± 26	82 ± 32	102 ± 21
Left layer	78 ± 23	54 ± 23 †	92 ± 19
Left ventricular	71 ± 21	71 ± 23	91 ± 18 †
Subendocardial	68 ± 20	46 ± 21 †	82 ± 23
Middle	75 ± 24	77 ± 26	96 ± 19
Subepicardial	71 ± 21	77 ± 24	92 ± 18

p< 0 05 (difference from control)
†p< 0 05 (difference between shunt groups)

ventricular free wall did not significantly change with direct shunts and increased approximately 30 per cent with indirect shunts (Fig 3) Coronary flow to the free wall of the right ventricle showed no significant change from control in either group Although total septal flow did not significantly change with direct shunts coronary flow to the left ventricular side of the septum fell significantly (Fig 4)

During the control state and the indirect A P shunts flow remained relatively homogeneous throughout the left ventricular free wall With direct A P shunts the coronary flow to the subendocardium decreased approximately 26 per cent of control while subepicardial coronary flow increased 12 per cent (Fig 3) When aortic diastolic pressure was maintained with the indirect shunts left ventricular subendocardial flow in

ventricular TTI was used to estimate changes in myocardial oxygen needs[10] We realize that the relationship between the TTI and myocardial oxygen uptake is affected by changes in ventricular volume as occurred in this study However left ventricular stroke volume and left atrial pressures were not significantly different between the two types of A P shunting suggesting that the ventricular volumes were comparable During direct A P shunts the left ventricular TTI did not change but coronary flow to the subendocardium decreased. When the coronary driving pressure was increased during indirect A P shunts left ventricular subendocardial flow and TTI both increased. Since coronary vessels normally autoregulate flow relative to myocardial oxygen needs the decrease in left ventricular subendocardial flow with the direct A P shunts suggests that regional underperfusion occurred. In a recent abstract Vincent and associates[15] reported similar findings in their studies of aortopulmonary shunts i e although total left ventricular coronary flow increased, the subendocardial muscle became relatively underperfused as evidenced by a fall in the ratio of subendocardial subepicardial flow to 0 7 1

In previous studies of left ventricular subendocardial ischemia the relationship between the DPTI and the TTI was of predictive value in recognizing when coronary maldistribution occurred.[11] Those studies were performed in open chest anesthetized dogs, in which aortic diastolic pressure had been decreased by opening arteriovenous fistulas. When the ratio of DPTI/TTI was above 0 80 the left ventricular free wall was evenly perfused. The present study and that of Vincent and colleagues[15] verify the usefulness of those indices in predicting the occurrence of subendocardial underperfusion The DPTI/TTI ratio averages 0 35 in the direct shunt group in which subendocardial flow fell whereas the ratio averaged 0 66 (not statistically different from 0 80) with the indirect shunts in which left ventricular flow was homogeneous.

In this study left ventricular outputs and shunt flows were kept constant in both types of A P shunts to determine if the volume load was a factor in reducing coronary flow Our data indicate that it was not the magnitude of the shunt which altered coronary perfusion but the fall in diastolic coronary driving pressure Since left ventricular diastolic pressure did not change significantly, the drop in diastolic coronary driving pressure resulted from the changes in aortic diastolic pressure This means that under these conditions changes in the coronary driving pressure for the subendocardial region of the left ventricle may be estimated from the mean aortic diastolic pressure (aortic diastolic pressure time index) Therefore pressure indices of myocardial oxygen supply and demand may be calculated from pressure tracings recorded in the operating room The ratio of aortic diastolic pressure time index/LV tension time index (aortic mean diastolic pressure diastolic period/aortic mean systolic pressure systolic period) may be of value in identifying when an A P shunt procedure is likely to result in subendocardial underperfusion Under such circumstances coronary perfusion may be improved by either reducing the size of the anastomosis or increasing aortic diastolic pressure

Summary

Changes in regional coronary hemodynamics during A P shunting were studied in open chest anesthetized dogs During direct A P shunting coronary driving pressure fell which resulted in decreased coronary flow to the subendocardial region of the left ventricle and abnormal coronary reactive hyperemic responses When aortic diastolic pressure was augmented during indirect A P shunting underperfusion of the subendocardial region was corrected and the coronary hyperemic responses returned to normal Since shunt flows were equal in both groups the magnitude of the shunt was not a factor in reducing coronary flow The present study indicates that acute A P shunts may cause underperfusion of the left ventricular subendocardium Thus under these conditions the left ventricle is stressed by a combination of an increased workload in the face of reduced subendocardial coronary flow

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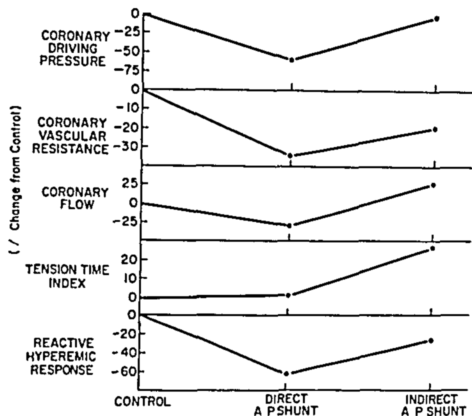


Fig 5 Changes in coronary hemodynamics in the subendocardial region of the left ventricle Asterisk indicates significant difference ($p < 0.05$) between adjacent points.

0 35 ± 0 09 with direct A P shunts This ratio increased to 0 66 ± 0 12 during the indirect A P shunts when coronary flow to the subendocardium significantly increased.

Discussion

Creation of A P shunts results in an abrupt fall in aortic diastolic pressure[7,8] Such a change in pressure may have a greater effect on coronary flow to the left ventricular subendocardium since its perfusion occurs almost entirely during diastole Coronary flow to the subepicardium is not as dependent upon diastolic pressure since it is perfused during both systole and diastole These phasic differences in regional coronary flow are probably due to the dissimilarity in regional coronary driving pressure In the subendocardium the intramyocardial pressure is nearly equal to left ventricular pressure This means that, during systole coronary driving pressure in the subendocardium approaches zero, making flow to this region more dependent upon diastolic hemodynamics The diastolic coronary driving pressure in the subendocardium has been graphically represented as the area between the aortic and left ventricular pressure tracings (Fig 1)[11] Any hemodynamic change which reduces this area such as shortening diastole increasing left ventricular diastolic pressure, or decreasing aortic diastolic pressure lowers the coronary driving pressure in this region With direct A P shunts coronary driving pressure abruptly fell due to the decrease in aortic diastolic pressure This resulted in a decrease in coronary perfusion to the subendocardial region of the left ventricle Under these conditions, the postocclusive reactive hyperemic responses of the left anterior descending coronary artery were abnormal payback accounted for only 84 per cent of the flow debt indicating a marked reduction in coronary vasomotor reserve The indirect A P shunts had higher aortic diastolic pressures, thereby maintaining coronary driving pressure and increasing coronary flow to the subendocardium Coronary reserve was significantly improved as evidenced by the postocclusive hyperemic payback being 156 per cent of the flow debt. Therefore, even with the same shunt flow, when aortic diastolic pressure was increased coronary perfusion to the subendocardium was augmented

Alterations in coronary flow become more meaningful when they are related to changes in myocardial oxygen needs In this study the left

ventricular TTI was used to estimate changes in myocardial oxygen needs[10] We realize that the relationship between the TTI and myocardial oxygen uptake is affected by changes in ventricular volume as occurred in this study However left ventricular stroke volume and left atrial pressures were not significantly different between the two types of A P shunting suggesting that the ventricular volumes were comparable During direct A P shunts the left ventricular TTI did not change but coronary flow to the subendocardium decreased. When the coronary driving pressure was increased during indirect A P shunts left ventricular subendocardial flow and TTI both increased Since coronary vessels normally autoregulate flow relative to myocardial oxygen needs the decrease in left ventricular subendocardial flow with the direct A P shunts suggests that regional underperfusion occurred. In a recent abstract Vincent and associates[15] reported similar findings in their studies of aorticopulmonary shunts i e although total left ventricular coronary flow increased, the subendocardial muscle became relatively underperfused as evidenced by a fall in the ratio of subendocardial subepicardial flow to 0 7 1

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Table I Effect of smoking cigarettes on epinephrine and norepinephrine content in the serum of habitual smokers (results expressed as nanograms per milliliter and given as mean ± standard error)

	Initial rest period (min.)				Time after smoking (min.)			
	10		40		1		10	
	E*	NE*	E	NE	E	NE	E	NE
Non nicotine cigarette	0 63±0 09	0 63±0 12	0 40±0 05	0 42±0 06	0 47±0 06 (0 07±0 02)†	0 38±0 06	0 42±0 04	0 40±0 07
0 3 mg of nicotine per cigarette	0 47±0 05	0 39±0 04	0 32±0 04	0 42±0 07	0 47±0 05‡ (0 15±0 08‡)†	0 48±0 05	0 33±0 04	0 38±0 09
1 09 mg of nicotine per cigarette	0 84±0 30	0 61±0 10	0 40±0 04	0 55±0 13	0 64±0 09‡ (0 25±0 07‡)†	0 66±0 06	0 40±0 04	0 59±0 06
2 73 mg of nicotine per cigarette	0 64±0 10	0 78±0 20	0 30±0 04	0 43±0 07	0 81±0 06§ (0 50±0 04§)†	0 43±0 11	0 51±0 06	0 49±0 08

E, Epinephrine NE, norepinephrine
†Mean and standard error determined on the individual differences in epinephrine level between samples taken 40 minutes and 1 minute after smoking
‡P ≤ 0 05 §P ≤ 0 01

were centrifuged at 5 000 r p m the serum was decanted the protein was precipitated centrifuged at 30 000 r p m and then frozen until analyzed

NE and E were determined fluorometrically with the use of the method of Griffiths and associates[13] The serum catecholamines were concentrated and purified by selective absorption on alumina at pH 8 5 The catecholamines were then oxidized to their chrome derivatives with iodine and, after alkaline sulfite treatment the trihydroxyindole derivatives were estimated in an Aminco Bowman spectrophotofluorometer Great care is necessary during the purification of the alumina and in the subsequent absorption steps since small deviations from the stated pH s cause major inaccuracies

Initially the total corticoids were estimated in the plasma with the use of an ethanol-sulfuric acid reagent after an initial isooctane extraction[14] Subsequently cortisol and corticosterone were estimated by the method of Martin and Martin,[15] which has recently been shown to be one of three reliable methods to estimate corticoids[16] Comparison of the two methods showed that the latter method gave values which were consistently 10 per cent greater The FFA were estimated by a modification of the method of Duncombe[17]

Results

Each cigarette was marked so that it would be smoked to a 30 mm butt. Assuming a 90 per cent absorption of nicotine from the inhaled smoke smoking cigarettes with low intermediate and high nicotine content, the subject received 0 0 35 1 27, and 3 19 mg of nicotine respectively, per two cigarettes smoked The mean level of serum cholesterol of the subjects was 188 ± 8 1 mg per 100 ml and that of triglyceride was 113 ± 0 7 mg per 100 ml

After the 40 minute rest sitting to simulate the normal position of a sedentary smoker the NE and E values were comparable with those reported by Carruthers and associates[1] but were up to ten times higher than those found by Griffiths and Leung[18] in recumbent subjects The mean values obtained from the 12 subjects were similar on the four different visits when the blood was sampled (Table I) During the initial rest period the NE and E were reduced

No significant increase in the E or NE levels occurred in subjects smoking nicotine free cigarettes (Table I) After smoking two low

Table II Effect of smoking two cigarettes on catecholamine and FFA content in serum

	Initial rest period (min.)		Time after smoking (min.)	
	10	40	1	10
Volunteer F Z (48 yr) (male)				
1 *Nicotine cigarette*				
Epinephrine	1 07	0 75	1 28(53)‡	0 61
Norepinephrine	1 26	0 66	0 67	0 77
FFA	188	174	–	162
2† Epinephrine	0 46	0 31	0 89(58)‡	0 39
Norepinephrine	0 65	0 53	0 58	0 52
FFA	138	142	–	204(62)§
Volunteer S A (44 yr) (female)				
1 *Nicotine cigarette**				
Epinephrine	0 44	0 33	1 16(83)‡	0 39
Norepinephrine	1 20	0 43	–	0 10
FFA	510	630		675(45)§
2† Epinephrine	1 10	0 23	0 93(70)‡	0 49
Norepinephrine	0 16	0 41	0 13	0 35
FFA	346	366	–	370(4)§

*2 73 mg of nicotine per cigarette two cigarettes smoked per test.
†Cigarettes smoked on different days
‡Difference in epinephrine level (ng/ml.) prior to and one minute after smoking
§Difference in FFA (μEq/liter) before and 10 minutes after smoking

nicotine (0 29 mg) cigarettes the E level increased significantly from 0 32 to 0 47 *ng per* milliliter while the NE level was unaltered. A greater elevation of E occurred on smoking two high nicotine (2 73 mg) cigarettes (0 30 to 0 81 ng per milliliter but the NE level remained unaltered. The increase in the nicotine content from 0 to 2 73 mg per cigarette appeared to cause a progressive rise of the serum E To investigate this dose response further three cigarettes with an intermediate nicotine content of 1 09 mg were smoked consecutively by subjects The catecholamine levels were found to fall between the high and low nicotine cigarettes For example subject F Z. smoking first two and then three intermediate and lastly two high nicotine cigarettes showed increases in the E level of 18 31 and 58 per cent, respectively and subject F S showed increases of 8 26 and 36 per cent, respectively The increase in the E shown in Table II in two representative subjects smoking high nicotine cigarettes was reproducible although the initial E content varied from day to day In regard to change in the FFA no relationship to the nicotine content or the serum E level was evident. The FFA in some subjects varied from day to day and between subjects As shown in Table III where the percentage increase in FFA is given for the mean values of each group of 12 subjects no dose response is evident

The serum corticoids were increased only after smoking the high nicotine cigarettes (Table IV) The serum corticoids increased only after a 10 *minute delay* and had a prolonged elevation unlike the rapid rise and fall of E on smoking Also both cortisol and corticosterone were *increased* with the high nicotine cigarette (Table IV) After smoking five cigarettes containing 1 09 mg of nicotine per cigarette the cortisol content was increased approximately twofold but this increase varied with the individual

On prolonged smoking (of five high nicotine cigarettes) the elevated cortisol level was further increased compared with the elevation obtained after smoking two cigarettes (Table V) It should be noted that the serum corticoid values when initially high on arrival often decreased rapidly during the rest period (Table IV)

Discussion

The observed elevation of serum epinephrine and corticoids on smoking cigarettes and their

Table I Effect of smoking cigarettes on epinephrine and norepinephrine content in the serum of habitual smokers (results expressed as nanograms per milliliter and given as mean ± standard error)

	Initial rest period (min.)				*Time after smoking (min.)*			
	10		*40*		*1*		*10*	
	*E**	*NF**	*E*	*NE*	*E*	*NE*	*E*	*NE*
Non nicotine cigarette	0 63±0 09	0 63±0 12	0 40±0 05	0 42±0 06	0 47±0 06 (0 07±0 02)†	0 38±0 06	0 42±0 04	0 40±0 07
0 3 mg of nicotine per cigarette	0 47±0 05	0 39±0 04	0 32±0 04	0 42±0 07	0 47±0 05‡ (0 15±0 08‡)†	0 48±0 05	0 33±0 04	0 38±0 09
1 09 mg of nicotine per cigarette	0 84±0 30	0 61±0 10	0 40±0 04	0 55±0 13	0 64±0 09‡ (0 25±0 07‡)†	0 66±0 06	0 40±0 04	0 59±0 06
2 73 mg of nicotine per cigarette	0 64±0 10	0 78±0.20	0 30±0 04	0 43±0 07	0 81±0 06§ (0 50±0 04§)†	0 43±0 11	0 51±0 06	0 48±0 08

E, Epinephrine NE, norepinephrine
†Mean and standard error determined on the individual differences in epinephrine level between samples taken 40 minutes and 1 minute after smoking
‡$P \leq 0\ 05$ §$P \leq 0\ 01$

were centrifuged at 5 000 r p m the serum was decanted the protein was precipitated centrifuged at 30 000 r p m and then frozen until analyzed

NE and E were determined fluorometrically with the use of the method of Griffiths and associates[13] The serum catecholamines were concentrated and purified by selective absorption on alumina at pH 8 5 The catecholamines were then oxidized to their chrome derivatives with iodine and after alkaline sulfite treatment the trihydroxyindole derivatives were estimated in an Aminco Bowman spectrophotofluorometer Great care is necessary during the purification of the alumina and in the subsequent absorption steps since small deviations from the stated pH s cause major inaccuracies

Initially, the total corticoids were estimated in the plasma with the use of an ethanol-sulfuric acid reagent after an initial isooctane extraction[14] Subsequently cortisol and corticosterone were estimated by the method of Martin and Martin[15] which has recently been shown to be one of three reliable methods to estimate corticoids[16] Comparison of the two methods showed that the latter method gave values which were consistently 10 per cent greater The FFA were estimated by a modification of the method of Duncombe[17]

Results

Each cigarette was marked so that it would be smoked to a 30 mm butt Assuming a 90 per cent absorption of nicotine from the inhaled smoke smoking cigarettes with low, intermediate and high nicotine content, the subject received 0 0 35 1 27 and 3 19 mg of nicotine respectively per two cigarettes smoked The mean level of serum cholesterol of the subjects was 188 ± 8 1 mg per 100 ml and that of triglyceride was 113 ± 0 7 mg per 100 ml

After the 40 minute rest sitting to simulate the normal position of a sedentary smoker, the NE and E values were comparable with those reported by Carruthers and associates[12] but were up to ten times higher than those found by Griffiths and Leung[18] in recumbent subjects The mean values obtained from the 12 subjects were similar on the four different visits when the blood was sampled (Table I) During the initial rest period the NE and E were reduced

No significant increase in the E or NE levels occurred in subjects smoking nicotine free cigarettes (Table I) After smoking two low

Table V Serum corticoids in volunteers smoking cigarettes containing 2 73 mg of nicotine
A Volunteers smoked two cigarettes

	Prior to smoking (min)		*Time after smoking (min)*		
	10	*40*	*1*	*10*	*20*
Cortisol (6)	ᴗ8 ±0 9	4 6 ±0 5	6 9 ±1 3	11 6 ±0 9†	11 3 ±1 8†
Corticosterone (6)	0 6 ±0 01	0 6 ±0 01	0 8 ±0 2	1 6 ±0 2†	1 8 ±0 3†

B Volunteers smoked two cigarettes followed by an additional three cigarettes at 10 minute intervals

	Rest period 40 min	*Time after smoking*		
		2 cigarettes 10 min.	*5 cigarettes*	
			10 min.	*20 min.*
Cortisol (6)	5 50 ±0 46	10 6 ±1 04†	16 5 ±1 6ᴗ†	16 0 ±3 06†
Corticosterone (6)	0 60 ±0 08	1 2 ±0 22‡	2 5 ±0 33‡	1 9 ±0 4§

N mbe f ubjects per gr up (co t c ds det rm ned by th m thod of Martin nd Mart n[15])
†P ≤ 0 01
‡P ≤ 0 05

dium with subsequent release of FFA from adipose tissue[26] or it may act directly on the sympathetic nervous system [27] In this study no relationship between the increase in E content and the subsequent increase in FFA in the serum was evident Although Kershbaum and associates[28] reported a variable increase in the FFA after smoking as well as between individuals Frankl and colleagues[29] failed to find any significant increase in FFA after smoking The fact than no increase occurred in FFA with increasing nicotine exposure suggests that FFA do not account for epidemiologic findings showing a dose response of cigarette smoking to cardiovascular events

In regard to the effects of stress Friedman and associates[30] have suggested that the cortisol concentration is higher in coronary prone subjects Moss and co workers[31] reported that adrenal stress response noted by increased plasma cortisol levels and the presence of ventricular premature beats were reliable pre hospital precursors of ventricular arrhythmias Furthermore in high risk middle aged sedentary men Blackburn and colleagues[32] reported that exercise decreased the incidence of ectopic beats

The relationship of an elevation of corticoids to atherosclerosis or any specific cardiovascular change is as yet undefined It has been suggested that corticoids may sensitize the myocardium to the effect of catecholamines [10] The effect of daily elevation of serum corticoids with prolonged smoking of high nicotine cigarettes on the normal diurnal rhythm of corticoid secretion remains to be determined.

If epidemiologic studies should show that smokers of low nicotine cigarettes have a lower rate of myocardial infarction than smokers of a comparable number of high nicotine cigarettes it would further implicate the importance of nicotine and consequently of E and/or corticoids in the pathogenesis of myocardial infarction Since low and high nicotine cigarettes produce an equal amount of carbon monoxide [33] such epidemiologic findings would support the concept that nicotine rather than carbon monoxide enhances the risk of a coronary event

While a study of acute phenomena can provide leads for the development of less harmful cigarettes it remains for epidemiologic studies to show how different ways of inhalation and the smoking of various tobacco products are associated with different risks for cardiovascular events The magnitude of the cardiovascular disease problem and the apparent fact that cigarette smoking remains a common habit demand that we increase collaborative laboratory and epidemiologic studies in a specific aim toward less harmful smoking products

Table III Percentage increase in serum FFA after smoking cigarettes containing different amounts of nicotine

	Time after smoking two cigarettes	
	1 min. (% increase in FFA)	*10 min. (% increase in FFA)*
Non nicotine cigarette*	6 3	11 2
0 3 mg of nicotine per cigarette	31 3	46 3
1 09 mg of nicotine per cigarette	40 6	33 2
2 73 mg of nicotine per cigarette	21 6	28 4

Twelve subjects per group each group contains same subjects

Table IV Changes in serum corticosteroids in volunteers after smoking two cigarettes containing different amounts of nicotine

	Resting period (min)		*Time after smoking (min.)*	
	10	*40*	*1*	*10*
Non nicotine cigarette	7 3 ±0 7	6 3 ±0 6	6 7 ±0 8	6 6 ±0 7
0 3 mg of nicotine per cigarette	9 1 ±0 7	7 8 ±0 6	7 8 ±0 7	7 8 ±0 7
1 09 mg of nicotine per cigarette	8 8 ±0 4	7 7 ±0 5	7 7 ±0 7	8 5 ±0 8
2 73 mg of nicotine per cigarette	9 0 ±1 3	7 4 ±0 7	9 1 ±1 4	11 9 ±1 3†

Twelve subjects per group (determined by method of Givner and Rochefort[14])
†P ≤0 01

relationship to the nicotine content of the cigarette is of significance since epidemiologic evidence indicates a dose response of myocardial infarction to the inhalation of tobacco smoke containing nicotine and other substances

The marked elevation of serum epinephrine due to smoking found in this study supports the findings of Watts[19] but is in disagreement with the results of Klensch [20] who reported an increase in norepinephrine on smoking Where subjects were allowed to smoke without a preliminary rest the epinephrine level was not statistically increased (prior to smoking 1 58 ±0 26 nanograms per milliliter, one minute after smoking 2 27 ± 0 51 nanograms per milliliter 18 subjects) The different conditions of our procedure relating to the rest period and smoke inhalation as compared to those reported by Tucci and Sode[21] may explain why they failed to find any significant change in these parameters on smoking

As reported by Vendsalu [22] catecholamine values taken sitting are considerably higher than those taken in a recumbent position, which may explain the differences between our base line data and those found by Griffiths

Although basal levels of catecholamines vary with the method of analysis [3] Carruthers and colleagues[12] give a mean value of 0 28 µg per liter (range of values 0 01 to 1 89) for E and 0 79 µg per liter (range of values 0 17 to 3 26) for NE for healthy subjects In this study, changes in the E content in sitting subjects on smoking were reproducible in each subject and as reported by Carruthers and his group, inaccuracies involved were those showing falsely low values

Elevated serum levels of NE are often associated with arrhythmias but their relationship remains unproved [24] No correlation between time of elevation of plasma catecholamine and the presence of ventricular arrhythmias is apparent [25]

The mechanism by which cigarette smoking may affect cardiovascular events has received much discussion It has been postulated that nicotine may exert its effect on the myocardium either by release of catecholamines from the adrenal medulla or directly from the myocar-

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A Volunteers smoked two cigarettes

	Prior to smoking (min.)		*Time after smoking (min)*		
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Corticosteron (6)	0 6 ±0 01	0 6 ±0 01	0 8 ±0 2	1 6 ±0 2†	1 8 ±0 3†

B Volunteers smoked two cigarettes followed by an additional three cigarettes at 10 minute intervals

	Rest period 40 min	*Time after smoking*		
		2 cigarettes 10 min.	*5 cigarettes*	
			10 min	*20 min.*
Cortisol (6)	5 50 ±0 46	10 6 ±1 04†	16 5 ±1 65†	16 0 ±3 06†
Corticosterone (6)	0 60 ±0 08	1 2 ±0 22‡	2 5 ±0 33‡	1 9 ±0 48

Numbe of s bjects per g oup (co t c ds dete mi ed by the method f Mart n and Martin[15])
†P ≤ 0 01
‡P ≤ 0 05

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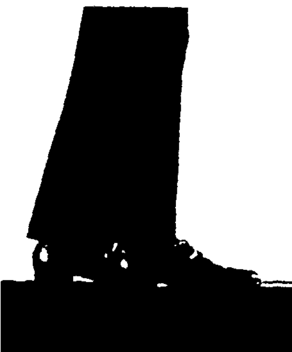
Summary

After a 40 minute rest in a sitting posture the catecholamines, corticoids, and FFA levels in the serum were determined prior to and after smoking cigarettes under standard conditions of inhalation Increasing the nicotine content in the smoke progressively increased the epinephrine—but not the norepinephrine—content in the serum Increasing the number of low nicotine cigarettes smoked also led to an elevation of epinephrine The serum corticoids were markedly elevated on smoking high nicotine cigarettes The FFA changes were not related to either the amount of nicotine inhalation or the elevation of serum E The possible epidemiologic implications of these findings were briefly discussed

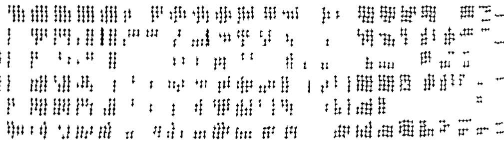
The authors thank Ms Luba Garbaczewski for her assistance

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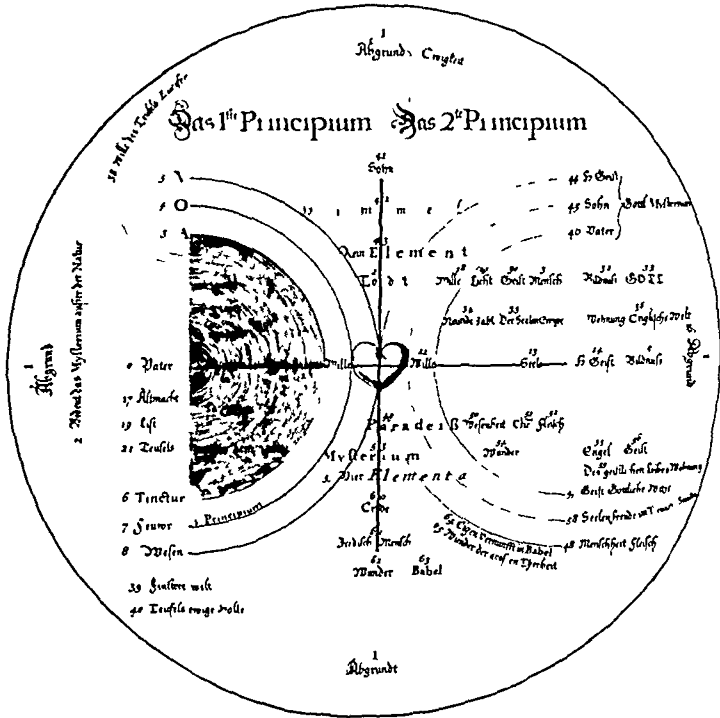
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Precautions Do periodic serum electrolyte and BUN determinations Do periodic hematologic studies in cirrhotics with splenomegaly Antihypertensive effects may be enhanced in post sympathectomy patients The following may occur hyperuricemia and gout reversible nitrogen retention descreasing alkali reserve with possible metabolic acidosis hyperglycemia and glycosuria (diabetic insulin requirements may be altered) digitalis intoxication (in hypokalemia) Use cautiously in surgical patients Concomitant use with antihypertensive agents may result in an additive hypotensive effect

Adverse Reactions Muscle cramps weakness dizziness headache dry mouth anaphylaxis rash urticaria photosensitivity purpura other dermatological conditions nausea and vomiting (may indicate electrolyte imbalance) diarrhea constipation other gastrointestinal disturbances Rarely necrotizing vasculitis paresthesias icterus pancreatitis and xanthopsia have occurred with thiazides alone

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Disappearance of right bundle branch block with left anterior hemiblock when associated with a type B pre-excitation syndrome

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In an analysis of 100 000 electrocardiograms (ECG s) Pick and Fisch[1] found association of bundle branch block and the pre excitation syndrome in 0 24 per cent of the cases There are quite a few publications showing this association but few reports have demonstrated the coexistence of pre excitation and left anterior hemiblock (LAH) or left posterior hemiblock (LPH) In Massumi s[2] case a type A Wolff Parkinson White syndrome (WPW) was associated with right bundle branch block (RBBB) and LPH

This article presents a case of LAH and RBBB coexisting intermittently with a type B pre excitation masking the bifascicular block

Case report

F M T a 46 year old man had an episode of acute polyarticular rheumatism at the age of 15 He was asymptomatic until the age of 42 when progressive dyspnea bronchitis and hemoptysis began he occasionally complained of palpitations

On admission to the hospital on Sept 25 1971 his disease was diagnosed as calcific mitral stenosis and pulmonary hypertension systolic pressure of pulmonary artery 60 mm Hg) On Oct 13 1971 his mitral valve was replaced with a Beall prosthesis A year later he was reoperated upon because of partial detachment of the prosthesis which was replaced with a Bjork valve In both operations a demand pacemaker was inserted to prevent an atrioventricular (A V) block At present he is asymptomatic

The electrocardiogram (ECG) on admission showed sinus rhythm and ventricular complexes with different configurations alternating with the same P P and R R interval The most frequent complex showed a configuration of advanced RBBB and LAH (AQRS−50 rsR in Lead V_1 Rs in V_5 and V_6 q in I and aV_L) the P R interval was 0 12 sec The other complex had a configuration of type B WPW (negative complexes in V_1 and positive in V_5 and V_6 with negative and positive delta waves respectively positive delta wave in I II and aV_L and a negative in aV_R AQRS =0 and QRS = 0 12 sec) the P R interval was 0 16 sec (Figs 1 to 3)

At the end of both operations a temporary period of bradycardia or A V block might have occurred because the pacemaker functioned on demand In the postoperative period a short period of supraventricular tachycardia occurred (Fig 4)

In all the ECG s taken since operation until now the image of RBBB plus LAH has persisted and no pre-excitation complexes have been found (Fig 5)

Discussion

The ECG configurations of RBBB and LAH are well established The image of RBBB is evident in the horizontal plane and the LAH in the frontal plane with the addition of the effects of the RBBB in the last 0 04 sec[3-5]

In our case a characteristic pattern of RBBB plus LAH was recorded in all pre and postoperative tracings (three years of observation) This pattern disappeared only when type B pre excitation was associated thus indicating the chronicity of the bifascicular block The ventricular complex with a type B pre excitation could be interpreted as a left bundle branch block (LBBB) originated by an intermittent LPH in the presence of a fixed LAH but this hypothesis is discarded because logically a complete or incomplete A V block should have been produced This did not occur rather on the contrary the P R interval decreased If we accept

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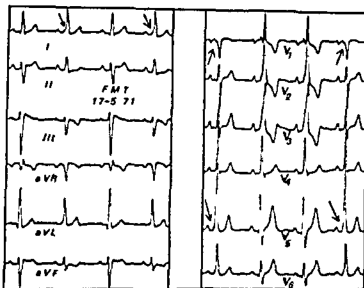


Fig 1 Alternating ventricular complexes with different configurations The arrow indicates those with pre excitation

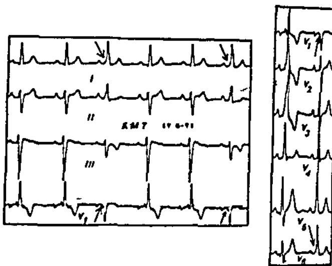


Fig 2 Simultaneous tracing of Leads I II III and V_1 Masking of RBBB and LAH can be seen when an added pre excitation exists

that it was LBBB the other possibility would be the intermittent disappearance of the RBBB when LBBB appeared but this is improbable with such an advanced and persistent RBBB

These observations together with the absence of alterations in the repolarization such as those found in the advanced LBBB and the presence of delta waves and the rest of the QRS complex, as described in type B WPW[6] reinforce the hypothesis that these complexes are produced by the type B pre excitation associated with RBBB plus LAH On the other hand the P R interval although it remained within normal limits was shorter than when RBBB and LAH alone existed

Several studies have pointed out that in the presence of a RBBB the addition of a type B pre excitation masks the image of the RBBB[7,9] The delay in the depolarization of the right ventricle—a consequence of the bundle branch block—is eliminated when a premature excitation of this ventricle occurs with the RBBB image thereby disappearing In some cases like the one described by Robertson and associates[10] in a patient with Ebstein s anomaly the association of a type B WPW did not mask the image of RBBB Cabrera and colleagues[11] also described cases with Ebstein s disease and this association with different ECG tracings Gersony and Ekery[9] think that in these cases the persistence of the RBBB image is probably the consequence of a localization of the block zone posterior to the pre excitation area In our case, the RBBB image was completely canceled when the type B pre excitation was associated indicating that the depolarization of the right ventricle mainly occurs from the pre excitation area

In the presence of LAH the first area activated is the posteroinferior zone of the left ventricle which gives rise to the q wave in Leads I and aV_L.[3] If a WPW is associated, logically the posteroinferior wall of the left ventricle will be activated after the pre excitation area and a delta wave is produced the orientation of which is determined by the site of pre excitation In the case of a type B WPW this site is located in the A V groove of the right ventricle as demonstrated experimentally by Durrer and Roos[12] The foregoing determines the delta waves being directed to the left and therefore replacing the q of I and aV_L of the LAH The rest of the depolarization of the left ventricle occurs in part due to the normal conduction system and in part through the pre excitation area

In our case stimulation by the normal conduction system is only through the posteroinferior division because a RBBB and LAH exist The bifascicular block produces an axis of −50° in the frontal plane The type B WPW usually deviates the axis to the left thereby frequently producing images similar to those of LAH[13] however this is variable because the limits usually oscillate between +30° and −45°[14] In our case the isolated WPW should probably produce an axis of around +40° which would explain why the sum with LAH produces an axis of 0

Therefore the most significant fact in the asso

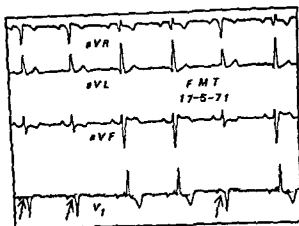


Fig 3 Simultaneous tracing of Leads aV_R aV_L, aV_F and V_1

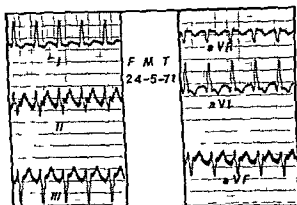


Fig 4 Supraventricular tachycardia (150 per minute) Complex configuration of RBBB and LAH

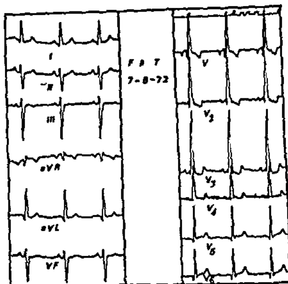


Fig 5 ECG tracing a year after the operation. The image of RBBB and LAH persists S wave in Leads V_5 and V_6 has decreased.

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Summary

A patient with mitral valve disease showing RBBB plus LAH with an intermittent association of type B pre excitation is presented.

The bifascicular block is masked by the existence of pre excitation The RBBB image is entirely canceled and the LAH is altered because its initial forces are replaced by a delta wave The electrical axis in the frontal plane is also modified

The mechanism of production of this ventricular complex is explained on the basis of the premature excitation of the right ventricle and the sum of forces produced by the activation through the posteroinferior division of the left bundle

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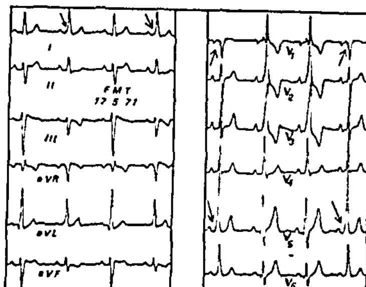


Fig 1 Alternating ventricular complexes with different configurations The arrow indicates those with pre excitation

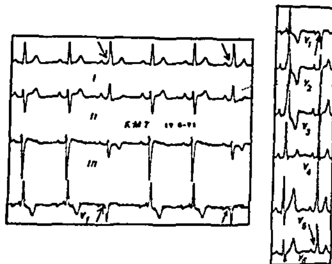


Fig 2 Simultaneous tracing of Leads I II III and V_1 Masking of RBBB and LAH can be seen when an added pre excitation exists

that it was LBBB the other possibility would be the intermittent disappearance of the RBBB when LBBB appeared but this is improbable with such an advanced and persistent RBBB

These observations together with the absence of alterations in the repolarization such as those found in the advanced LBBB and the presence of delta waves and the rest of the QRS complex as described in type B WPW[6] reinforce the hypothesis that these complexes are produced by the type B pre excitation associated with RBBB plus LAH On the other hand the P R interval although it remained within normal limits was shorter than when RBBB and LAH alone existed

Several studies have pointed out that in the presence of a RBBB the addition of a type B pre excitation masks the image of the RBBB[7,9] The delay in the depolarization of the right ventricle—a consequence of the bundle branch block—is eliminated when a premature excitation of this ventricle occurs with the RBBB image thereby disappearing In some cases like the one described by Robertson and associates[10] in a patient with Ebstein s anomaly the association of a type B WPW did not mask the image of RBBB Cabrera and colleagues[11] also described cases with Ebstein s disease and this association with different ECG tracings Gersony and Ekery[9] think that in these cases the persistence of the RBBB image is probably the consequence of a localization of the block zone posterior to the pre excitation area In our case, the RBBB image was completely canceled when the type B pre excitation was associated, indicating that the depolarization of the right ventricle mainly occurs from the pre excitation area

In the presence of LAH the first area activated is the posteroinferior zone of the left ventricle which gives rise to the q wave in Leads I and aV_L.[3] If a WPW is associated logically the posteroinferior wall of the left ventricle will be activated after the pre excitation area and a delta wave is produced the orientation of which is determined by the site of pre excitation *In the* case of a type B WPW this site is located in the A V groove of the right ventricle as demonstrated experimentally by Durrer and Roos[12] The foregoing determines the delta waves being directed to the left and therefore replacing the q of I and aV_L of the LAH *The rest of the* depolarization of the left ventricle occurs in part due to the normal conduction system and in part *through the pre excitation area*

In our case stimulation by the normal conduction system is only through the posteroinferior division because a RBBB and LAH exist The bifascicular block produces an axis of −50° in the frontal plane The type B WPW usually deviates the axis to the left thereby frequently producing images similar to those of LAH[13] however this is variable because the limits usually oscillate between +30° and −45°[14] In our case the isolated WPW should probably produce an axis of around +40°, which would explain why the sum with LAH produces an axis of 0°

Therefore the most significant fact in the asso

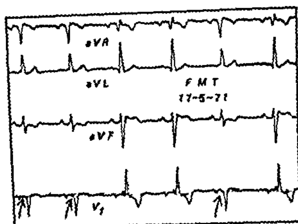


Fig 3 Simultaneous tracing of Leads aV_R aV_L, aV_F and V_1

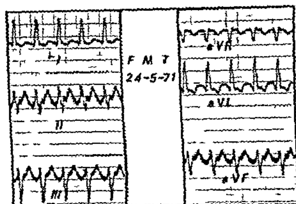


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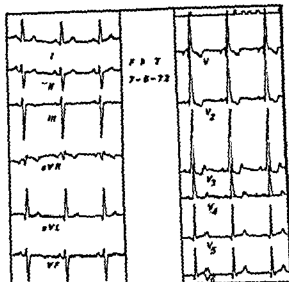


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Penicillium endocarditis following open heart surgery and prosthetic valve insertion

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The employment of mechanical devices to assist and sustain life in patients severely ill with cardiopulmonary disease and the clinical introduction of successive generations of anti microbial agents and immunosuppressive drugs have witnessed an increasing frequency of infec tions caused by opportunistic microorganisms Alterations in the balances of numbers among microorganisms indigenous to man and the im pairment of ordinary host defense mechanisms are likely factors in the ascendency of such in fections although it is by no means clear that other mechanisms are not also immediately in volved

Molds of the genus *Penicillium* are ubiquitous Thus it is surprising that only one instance of human penicilliosis has been recorded in the English medical literature The patient de scribed by Huang and Harris[1] was a 40 year old Negro male with acute lymphocytic leukemia whose rapidly fatal illness was complicated by pulmonary and central nervous system infection with *Penicillium commune*

The present repo t describes two patients with severe rheumatic heart disease who underwent cardiac valve replacement at the Maine Medical Center and whose postoperative courses were complicated by fatal endocarditis caused by a *Penicillium* species

Case reports

Case 1 In November 1970 a 56 year old Caucasian woman (MMC 118074) with rheumatic heart disease under went replacement of her aortic and mitral valves with Starr Edwards prostheses. Left and right heart catheterizations had previously demonstrated mitral insufficiency and stenosis and aortic insufficiency and stenosis. Surgery with the aid of cardiopulmonary bypass was accomplished with out incident and the patient received *cephalothin* in travenously for one week postoperatively She was di charged from the Maine Medical Center on December 15 1970 The patient was readmitted to the hospital on Decem ber 28 1970 because of fever headache and anorexia Car diopulmonary examination on admission was unchanged from that at the time of hospital discharge two weeks earlier and was within normal limits except for the presence of multiple prosthetic heart valve sounds. The patient s tem perature was 102 F The peripheral blood leukocytes num bered 28 600 cells per mm ^{3} of which 80 per cent were poly morphonuclear leukocytes 7 per cent were band forms 5 per cent were lymphocytes and 7 per cent were monocytes Microscopic pyuria was noted. Twelve blood cultures were obtained during the first and second hospital days and were subsequently noted to be sterile after incubation for 10 days A urine culture obtained at the time of hospitalization grew greater than 100 000 colonies of *Escherichia coli* per milliliter of urine Intramuscular kanamycin administra tion was instituted on the second hospital day for presumed acute pyelonephritis. On the third and fourth hospital days conjunctival and cu aneous petechiae were noted. Heart sounds remained unchanged from those observed on admis sion no cardiac murmurs were audible On the fourth hospi tal day kanamycin administration was discontinued and in travenous therapy with methicillin for presumed staphylococcal endocarditis was substituted. Despite anti microbial therapy and vigorous supportive measures fever and peripheral blood leukocytosis persisted and the patient died suddenly on the seventh hospital day

Postmortem examination was performed 18 hours after death Bulky tan grumous vegetations were found adheren to the atrial and ventricular surfaces of the mitral prosthesis almost occluding the mitral prosthetic lumen ar d similar bulky vegetations were adherent to the aortic valve prosthesis. Microscopic examination of t e heart valve vegetations demonstrated innumerable hyphae and cultures of the aortic and mitral valve vegetations yielded pure cultures of a *Penicillium* species No histologic evid nce of fungal infection of brain, lungs abdominal organs adrenal glands or kidneys was found.

Case 2 In December 1970 a R year old Caucasian man

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Fig 1 Patient two Ventricular surface aortic prosthetic valve demonstrating almost complete occlusion of the valve orifice



Fig 2 Patient two Aortic portion of Starr Edwards prosthesis

(MMC 118446) underwent left and right heart catheterizations because of progressive shortness of breath and chest pain A heart murmur had been noted by his physician four years prior to hospital admission Cardiac catheterization was accomplished without incident and demonstrated aortic stenosis and insufficiency On December 22 1970 the patient underwent cardiopulmonary bypass and replacement of his heavily calcified aortic valve with a Starr Edwards prosthesis He received cephalothin intravenously for three days postoperatively and was discharged from the hospital on December 31 1970 On January 4 1971 while bending to tie his shoe at home he experienced severe pain in the left calf The patient was readmitted to the Maine Medical Center on January 5 1971 and underwent immediate exploration of the left popliteal artery from which an embolus was extracted with subsequent prompt restoration of the circulation to the left leg The patient s temperature was 104 F at the time of hospital readmission and two conjunctival petechiae were observed by his physician The peripheral white blood cell count was 11 200 cells per mm^3 and the differential included 80 per cent polymorphonuclear leukocytes 10 per cent lymphocytes and 10 per cent monocytes The patients heart sounds were unchanged from those heard immediately after open heart surgery and his sternal wound was nicely healed Blood cultures were obtained these were subsequently reported to be sterile despite the patient having received no antibiotics during the 10 days preceding hospital readmission On the third hospital day reembolization to the left femoral artery occurred and again the patient underwent successful embolectomy with prompt restoration of circulation in the left leg By this time however additional petachiae had appeared and a presumptive diagnosis of staphylococcal endocarditis complicating open heart surgery and prosthetic valve insertion was made Intravenous methicillin therapy was instituted On the fifth hospital day despite methicillin administration and anticoagulation with heparin the patient experienced a cerebrovascular accident resulting in loss of consciousness and right hemiplegia The patient died on the tenth hospital day Prior to death fungal hyphae were reported present in histologic sections of both emboli previously removed at surgery

Postmortem examination was performed 16 hours after death A friable bulky tan vegetation covered most of the ventricular portion of the prosthetic aortic valve and extended beyond the valve ring virtually occluding the aortic outflow tract (Figs 1 and 2) Microscopic examination of a portion of the valve vegetation demonstrated polymorphonuclear leukocytes and mononuclear cells and numerous septate hyphae (Fig 3) Culture of the heart valve vegetation on cornmeal and Litman agars at room temperature yielded numerous colonies characterized by concentric rings of grey green mold (Fig 4) composed of septate hyphae with terminal branching identified as *Penicillium* species (Fig 5)

Investigation

Immediate epidemiologic investigation of events surrounding the occurrence of two such unusual cardiac infections in close temporal proximity subsequently resulted in the identification of a ceiling ventilator heavily colonized with a *Penicillium* species 40 inches above the site of pump oxygenator assembly and priming in the pump assembly room Five of 14 operating rooms including the cardiac operating room harbored a *Penicillium* mold in their ventilation systems Only the ventilation duct in the pump assembly room however allowed cooled humidified cotton felt filtered air to be blown directly at a presumably sterile site Microbiological sampling of the pump oxygenator itself and of equipment employed in the cardiac operating room and in the cardiac



Fig 3 Patient two Aortic valve vegetation Numerous septate hyphae (Gomori stain Original magnification × 1000)

catheterization laboratory was unrewarding Careful analysis of both open heart surgical procedures revealed no likely means by which direct fungal contamination of the surgical field might have occurred Cardiac surgery which had been discontinued as soon as the significance of the heart valve infections became known was resumed after completion of the epidemiologic investigation and closure of the ceiling ventilator

Comment

Uys and associates[2] have described the first instance of fungal endocarditis following cardiac valve replacement Their patient was a 22 year old woman with mitral insufficiency as a consequence of rheumatic fever with carditis at age 11 years Her infection was caused by the fungus *Paecilomyces* an ordinarily nonpathogenic mold related to the species *Penicillium* Although Huang and Harris[1] subsequently described a case of acute disseminated penicilliosis in a 40 year old man farm worker with leukemia in 1963 further episodes of human infection due to *Penicillium* species have not been reported. When the ubiquity of this mold and the frequency with which cardiopulmonary bypass and postoperative assisted ventilation have been employed are considered, it is truly surprising that additional infections with *Penicillium* have not been reported Postoperative infections following cardiac valve replacement are most often bacterial[3,4] *Staphylococcus aureus* and *Staphylococcus epidermidis* have been the most frequently reported offending microorganisms but infections with Gram negative bacilli are known to occur with sufficient frequency so as to no longer merit reporting



Fig 4 *Penicillium* species colony Growth on cornmeal agar at room temperature × 5 days

Koelle and Pastor[5] in 1956 reported the first instance of fungal endocarditis complicating cardiac surgery Thirteen additional cases of fungal endocarditis complicating open heart surgery had been collected and reported by 1963[6] and in 1964 Newman and Cordell[7] published a report of endocarditis due to *Aspergillus fumigatus* in a 24 year old man following replacement of his mitral valve with a



Fig 5 *Penicillium* species Terminal branching septate hyphae (Original magnification ×100)

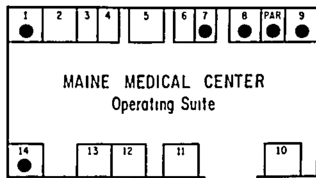


Fig 6 MMC Operative Suite *Room 9* is the cardiac operating room *PAR* is pump assembly room *Penicillium* species also recovered from ventilators in operating rooms *1 7 8* and *14*

Starr Edwards prosthesis In all 33 episodes of fungal endocarditis complicating prosthetic heart valve insertion have been reported previously [2 7 21] In one case report pertinent patient information was not recorded Characteristics of 32 patients with fungal endocarditis following cardiac valve replacement are noted in Table I Twenty seven patients were men and five were women Seven patients experienced fungal infection of their prosthetic mitral valves (six men and one woman) and 24 patients acquired fungal infection of a prosthetic aortic valve (21 men 3 women) One instance of *Candida* endocarditis complicating double valve replacement (aortic and mitral) has been previously recorded The role of offending microorganism has been equally divided between *Aspergillus* species and *Candida* species (14 cases and 16 cases respectively) One patient was infected with *Histoplasma capsulatum* and one with *Paecilomyces*.

Analysis of the clinical characteristics of fungal prosthetic heart valve infection (including the present case reports) shows that most patients have returned to their homes following surgery and have been reasonably well for approximately two months before becoming ill The mean duration from the date of heart valve replacement to death was 15 weeks (mode 8 weeks) the time between cardiac surgery and death due to fungal endocarditis ranged from 2 to 112 weeks Fourteen patients were known to have been febrile during their final illness and in all but two the maximum temperature during final hospitalization was greater than 101° F The peripheral white blood cell count was noted in eight case reports and ranged between 4 800 cells per mm^3 and 34 000 per mm^3 Three patients were noted to have hematuria or urinary red blood cell casts during their terminal illnesses Nine patients had premortem fungemia with an organism identical to that cultured from the prosthetic valve at autopsy only three patients are known to have had funguria with an identical organism Fifteen patients experienced major emboli to kidneys liver ovaries spleen and brain or experienced embolization of

femoral popliteal axillary brachial pulmonary or superior mesenteric arteries or saddle emboli of the aortic bifurcation Among eight patients who embolized their femoral or popliteal arteries five had emboli to the left femoral artery two to the left popliteal artery and one to the right popliteal artery In nine patients a new cardiac murmur was audible during the terminal febrile illness Three patients experienced congestive heart failure as a direct consequence of fungal endocarditis Cutaneous or mucous membrane petechiae and splenomegaly were observed in nine and four patients respectively

A variety of prosthetic heart valves was employed in patients experiencing postoperative fungal endocarditis Twenty two Starr Edwards valves were employed in 20 patients (two double prostheses) homograft valves were employed in eight patients Hufnagel and Shiley valves were each utilized in two patients and a mitral Ivalon baffle and an aortic Teflon prosthesis were each used in one patient In one patient the prosthetic valve was not described. Twenty three patients were known to have received postoperative antibiotic therapy No patient with *adequately documented* prosthetic heart valve fungal endocarditis survived infection.

Little information is available concerning the epidemiology of postoperative prosthetic fungal endocarditis Gage and colleagues[20] reported three instances of prosthetic heart valve infection due to an *Aspergillus* species and indicated a surgical suction device in introducing a sufficiently large fungal inoculum to initiate intracardiac infection during surgery Circumstantial evidence in the present report has implicated direct contamination of the pump oxygenator by air from an overhead ventilator

The unexpectedly high frequency with which male patients experienced prosthetic valve fungal endocarditis is not satisfactorily explained by available information Goodman and co workers[3] recorded a disproportionately high incidence of prosthetic bacterial endocarditis in adult males and bacterial blood stream invasion has been noted to occur twice as frequently in newborn males as in newborn females [22] Schlegel and Bellanti[23] have noted reduced leukocyte glucose 6 phosphate dehydrogenase activity in patients with chronic granulomatous disease of childhood and have suggested that a bimodal distribution of this X linked intracellular enzyme in males (who receive only a single maternal X chromosome) might result in diminished resistance to infection in some individuals Roth and Goldstein[24] noted an anti candida effect of normal human serum in 1961 This property of normal serum was subsequently shown to be a function of transferrin by Caroline and co workers[25] however neither group of authors noted any difference in transferrin mediated candidastatic activity in males and females Louria and co workers[26] have demonstrated a Candida clumping factor a macroeuglobulin of fast beta mobility in normal human sera and have observed interference with protective clumping activity by 7S IgG anti Candida precipitins and agglutinins Although information is not available regarding sex distribution of Candida clumping factor or Candida specific immunoglobulins Louria and co workers[27] have noted absent or reduced Candida clumping activity in the sera of fathers of three patients with endocrine hypofunction associated with mucocutaneous moniliasis Maternal Candida clumping activity was normal

Table I Fungal endocarditis in 32 patients following heart valve replacement

	Number of cases
Men (Mean age 39 1 years)	
Aortic valve	
Candida species	11 [8 9 11 17 19 21]
Aspergillus species	8 [12 13 16 20]
Histoplasma capsulatum	1 [10]
Paecilomyces	1 [2]
Mitral valve	
Candida species	1 [9]
Aspergillus species	5 [7 11 12 18 20]
Women (Mean age 44 1 years)	
Aortic valve	
Candida species	1 [12]
Aspergillus species	2 [15 _1]
Mitral valve	
Candida species	1 [14]
Aortic and mitral valves	
Candida species	1 [11]
	32

Sex linked host defense factors appear to be operative in some individuals and in certain types of infection The role of sex linked host defense mechanisms in patients with prosthetic heart valve fungal endocarditis however remains to be clarified

Summary

Two instances of postoperative prosthetic heart valve endocarditis caused by a *Penicillium* species occurred in a man and in a woman after replacement of aortic and aortic and mitral valves, respectively Prosthetic cardiac valve fungal endocarditis has been reported in 33 patients prior to the present report, in all but four instances infection was caused by a *Candida* species or by an *Aspergillus* species All reported patients with *adequately documented* prosthetic valve fungal endocarditis have died An inordinately high incidence of males is noted among patients with fungal prosthetic heart valve infection The basis for the apparently enhanced susceptibility of males to such infection remains to be clarified

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Pacemaker pseudodysfunction with a coronary sinus pacemaker

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Pacemaker pseudodysfunction is a well described entity resulting from multiple physiological and external physical events[1-6] Failure to recognize such phenomena may result in an unnecessary pacemaker battery or wire replacement Permanent pervenous atrial pacing from the coronary sinus is an established procedure for certain atrial and ventricular arrhythmias and the Sick Sinus Syndrome [7] The present report concerns a patient with a permanent transvenous coronary sinus pacemaker which demonstrated phenomena that initially incorrectly suggested pacemaker dysfunction

Case report

A ι8 year old Caucasian woman had permanent transvenous coronary sinus pacing effected with a Medtronic temporary demand generator (Model 5943) and electrode (Model 5818 18) July 3 1971 for Sick Sinus Syndrome The rate was set at ?2 beats per minute Subsequently the pacemaker always functioned as an atrial or as a ventricular pacemaker (Fig 1*A* and *B*) and at times functioned in both manners on the same rhythm strip (Fig 2) Deep respiration produced consistent cyclic variation in atrial and ventricular capture with ventricular capture occurring during deep inspiration and atrial capture during expiration (Fig 3) Normal breathing however produced no consistent change This caused slight variation of the ventricular rate due to the intermittent increase in the pacemaker artifact to QRS complex interval which occurred when the pacemaker functioned as an atrial pacemaker

A transtelephonic pacemaker testing service was used as one means of follow up Pacemaker spikes and digital pulsations are recorded by this method however the P waves and QRS complexes are not recorded. This testing method demonstrated for reasons described above variations in pacemaker artifact to digital pulse beat (Fig 4)

On October 28 1972 the patient was admitted to the hospital complaining of increasing dyspnea The electrocardiogram demonstrated atrial flutter with failure of the pacing artifact to capture the ventricle (Fig 5*A*) The position of the pacing catheter tip was unchanged on chest x ray (Fig 6) Following electrical cardioversion of the atrial flutter normal pacing resumed and has persisted (Fig 5*B*)

Discussion

Kitamura[8] reported both atrial and ventricular pacing with a temporary pacing catheter This was noted at the time of pacemaker insertion and the ventricular pacing appeared to be related to a higher current however it is possible such an association was fortuitous and may have resulted from slight movement of the catheter This temporary catheter later caused tamponade by myocardial perforation

Coronary sinus pacemakers may function either as an atrial or ventricular pacemaker depending on the site of the electrode tip in the coronary sinus [7,9] To our knowledge the present case is the only report of a permanent coronary sinus pacemaker functioning both as an atrial or as a ventricular pacemaker This type of pacing has been effective for 22 months and its *presence* does not necessarily indicate the need for electrode repositioning

Deep inspiration consistently caused ventricular pacing (Fig 3) most likely due to inspiratory withdrawal of the catheter in the coronary sinus. This is surprising since others have reported ventricular pacing with distal coronary sinus pacing [9]

Pseudopacemaker dysfunction may result from a variety of events which may simulate (1) battery failure (2) dysfunction of the demand

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Summary

Two instances of postoperative prosthetic heart valve endocarditis caused by a *Penicillium* species occurred in a man and in a woman after replacement of aortic and aortic and mitral valves respectively Prosthetic cardiac valve fungal endocarditis has been reported in 33 patients prior to the present report, in all but four instances infection was caused by a *Candida* species or by an *Aspergillus* species All reported patients with *adequately documented* prosthetic valve fungal endocarditis have died An inordinately high incidence of males is noted among patients with fungal prosthetic heart valve infection The basis for the apparently enhanced susceptibility of males to such infection remains to be clarified

The author is indebted to David L Adams M D Clement A Hiebert M D and Chris A Lutes M D for the opportunity to assist in the care of their patients described herein Mrs Edwin Gallant assisted in manuscript preparation

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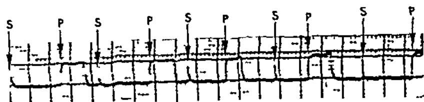
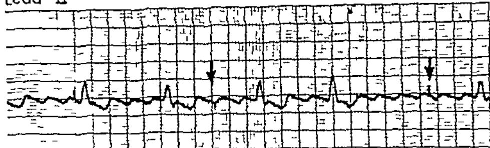


Fig 4 The pacemaker artifact is represented by a spike (S) and the digital pulsation by the broad deflection (P) Note the variation in the S P interval caused by intermittent atrial and ventricular pacing



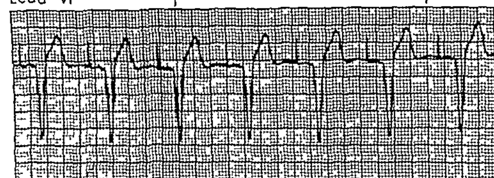


Fig 5 A and B A Atrial flutter with slow ventricular response Pacing artifact (*arrows*) fails to capture when clearly outside the ventricular refractory period. B Atrial pacing following electrical cardioversion of the atrial flutter

sensing unit, or (3) failure of the wire to deliver an adequate impulse to the myocardium [1,2] Battery failure is suspected when there is a slight pacemaker rate change Dysfunction of the demand sensing device is suggested if the pacing interval varies slightly in absence of competition Problems with delivery of an adequate impulse to the muscle are suggested when pacemaker artifact lying outside the ventricular refractory period fails to capture the myocardium This last event could be simulated in the present example especially with the present type of transtelephonic testing which cannot detect atrial activity

This type of transtelephonic pacemaker testing which records digital pulsatile flow and the pacing artifact is an established effective method of pacemaker follow up [10] Variation in the pacemaker artifact to digital pulsation could be interpreted by telephone testing as possible failure of the demand pacemaker to capture Electrocardiographic demonstration of intermittent atrial and ventricular capture on the same rhythm strip would produce an explanation for the variation detected transtelephonically However had only ventricular or atrial capture been observed on the same rhythm strip an explanation would not have been apparent and pacemaker rate variation would have been suspected This could have resulted in unnecessary replacement of the pacing unit.

Apparently this pacemaker was functioning as

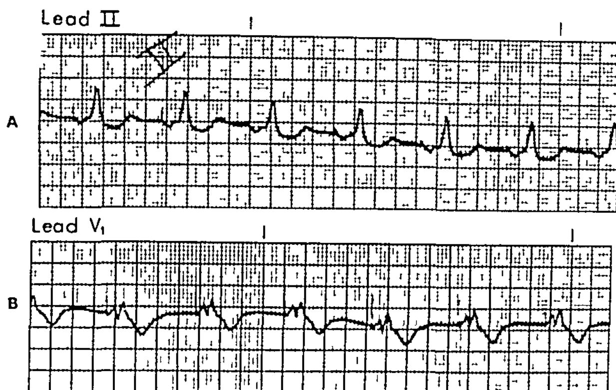


Fig 1 A and B *A* Pacemaker functioning as an atrial pacemaker *B* Pacemaker functioning as a ventricular pacemaker

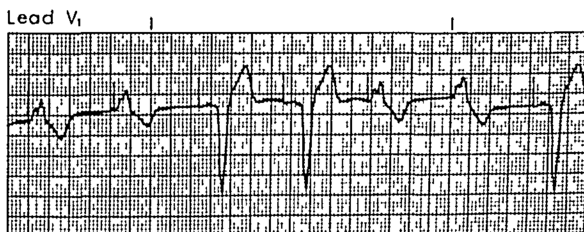


Fig 2 Pacemaker functioning as an atrial and ventricular pacemaker on the same rhythm strip

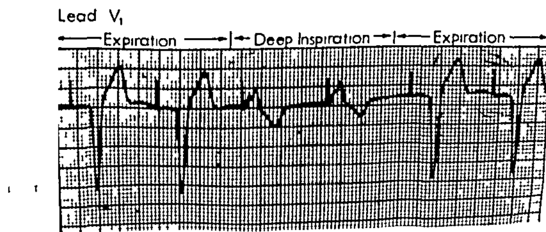


Fig 3 Deep respiration produced consistent cyclic variation in atrial and ventricular capture with ventricular pacing occurring during inspiration

Clinical pathologic conference

Frederic M Stone M D
F Blanton Bessinger M D
Kurt Amplatz M D
Rajendra Tandon M D
Jesse E Edwards M D
Minneapolis Minn.

DR FREDERIC M STONE A 3 month old boy was admitted to the University of Minnesota Hospitals on Nov 9 1972 because of rapid respirations poor feeding and poor gain in weight for three weeks He was the product of a term uncomplicated pregnancy and labor The mother was a 34 year old primigravida Birth weight was 3 130 grams At the initial examination after birth the infant was reported to be completely normal He exhibited no difficulties in the newborn nursery and was discharged to go home at three days of age He did well during the first month of life feeding without difficulty and apparently thriving At the age of one month examination showed no abnormalities and a gain of one pound The infant continued to be well during the second month of life

At the age of two months a systolic murmur at the left sternal border was described for the first time although no symptoms were noted No electrocardiogram (ECG) or thoracic roentgenogram was obtained on that visit Between the second and third months of life the parents noted increasing tachypnea and that he was irritable and diaphoretic during feeding

At three months of age he was seen for cardiac consultation at an affiliated hospital The abnormal findings included a Grade 3/6 pansystolic murmur and a Grade 2/6 diastolic flow murmur at the apex. Since the infant appeared to be in a state of congestive cardiac failure *elixir of digoxin* was administered, with 0 05 mg per kilogram of body weight as a total digitalizing dose Over the following week the infant exhibited no clinical improvement and was admitted to the University Hospitals for further study

On this admission the patient was small and acyanotic He weighed 3 900 grams and measured 56 5 cm Both weight and length were more than two standard deviations below the mean for his age The respiratory rate was 70 per minute and the cardiac rate was 170 per minute Simultaneous flush blood pressures in the right arm and right leg were 85 mm Hg Examination of the thorax revealed subcostal retractions but the lungs were clear to auscultation A systolic thrill was present along the left sternal border The first heart sound was of normal intensity Definite splitting of the second cardiac sound could not be appreciated No third or fourth heart sounds were heard A harsh holosystolic murmur Grade 4/6 was heard with maximal intensity at the lower left sternal border This murmur could be heard over the entire precordium A Grade 2/6 diastolic flow rumble was audible at the apex The liver was palpable 5 cm below the right costal margin in the midclavicular line The splenic tip was not palpable Pulses were equal in the brachial and femoral areas and were described as full. The remainder of the physical examination revealed normal conditions except for a right inguinal hernia

Hemoglobin was 13 4 Gm per 100 ml and the hematocrit reading was 39 per cent. Capillary blood gases obtained with the patient breathing room air revealed a pH of 7 48 a P_{CO_2} of 38 mm Hg and a P_{O_2} of 50 mm. Hg White blood count, urinalysis and concentrations of serum electrolytes and serum protein determined by electrophoresis were within normal limits Thoracic roentgenogram demonstrated generalized cardiomegaly and increased pulmonary vascularity (Fig 1) The ECG demonstrated QRS axis of + 95 degrees and left ventricular hypertrophy (Fig 2)

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Fig 6 Chest roentgenogram demonstrating catheter tip in the proximal coronary sinus

an atrial pacemaker at the time of atrial flutter and failed to capture because of almost constant atrial refractoriness It is also conceivable that ventricular pacing was inhibited at this time by Wedensky inhibition a phenomenon in which ventricular activation threshold is increased by atrial contraction [11,12] Transtelephonic testing at the time the patient was in atrial flutter with a slow ventricular rate would have been even more an indication of failure of the pacemaker to capture Atrial flutter could not be detected by the present telephonic system since only pacemaker discharge and digital pulsatile impulse are recorded

Pacemaker testing by telephone in our experience and others [10] is an effective method of assessing pacemakers on a 24 hour basis This service is particularly practical in rural areas However it should be appreciated that any system of pacemaker testing in which atrial and ventricular activity cannot be directly recorded has potential limitations

Summary

A permanent transvenous coronary sinus pacemaker functioned effectively for 22 months both as an atrial and ventricular pacemaker Slow atrial flutter resulted in failure of the pacemaker to capture the myocardium and thus incorrectly suggested pacemaker dysfunction Transtelephonic evaluation of this phenomenon was particularly difficult and could have resulted in unnecessary replacement of the pacing unit

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Clinical pathologic conference

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Fig 1 Frontal view of thoracic roentgenogram

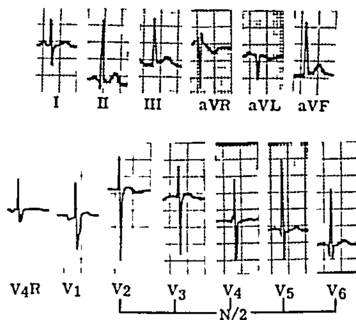


Fig 2 Electrocardiogram

Dr Bessinger will you please discuss the differential diagnosis?

DR F BLANTON BESSINGER The findings in this infant suggest rather severe acyanotic congenital heart disease Symptoms on admission were those of congestive cardiac failure with marked failure to thrive as well Sequence of the history was appearance of a systolic murmur at one to two months of age followed shortly by tachypnea and feeding difficulties—that is congestive cardiac failure This timing and sequence of events is typical of large left to right shunts In this type of congenital cardiac disease changes in pulmonary vascular resistance dictate the appearance

Table I Results of cardiac catheterization

Site	Pressure (mm. Hg)	O saturation (%)
Left atrium	a = 14 v = 15 m = 12	96
Right atrium	a = 6 m = 4	
Left ventricle	120/0 13	
Aorta	70/40 m = 55	88
Right ventricle	70/0	36

of murmurs and other symptoms [1] With maturation of the pulmonary arteriolar bed pulmonary vascular resistance characteristically falls Because of the timing of these changes in the newborn intracardiac left to right shunting does not occur to a significant degree until the affected infant is four to six weeks of age

The sequence of events therefore suggests a large left to right shunt Since a left to right shunt and congestive cardiac failure in early infancy usually involve a shunt at either the ventricular or the great vessel level the differential diagnosis includes ventricular septal defect, patent ductus arteriosus truncus arteriosus, atrioventricular canal and aorticopulmonary window

The physical findings of a loud pansystolic murmur at the left sternal border and a separate diastolic flow murmur at the apex suggest a ventricular septal defect but these types of murmurs are not incompatible with the other types of shunt lesions. The finding of sharp bounding pulses would suggest an aortic runoff lesion In this patient however the pulses were full and the absence of findings of a wide pulse pressure suggests that patent ductus arteriosus or aorticopulmonary window was not a primary lesion This finding also affects consideration of truncus arteriosus The presence of a single second sound might have suggested truncus arteriosus however, no ejection click was heard A further comment on the single second sound should be made Auscultation of a loud single second sound makes one consider the sound to be that of aortic closure as would be heard in truncus arteriosus corrected transposition of the great vessels complete transposition of the great vessels and tetralogy of Fallot Because of the absence of cya nosis I do not consider these latter two diag

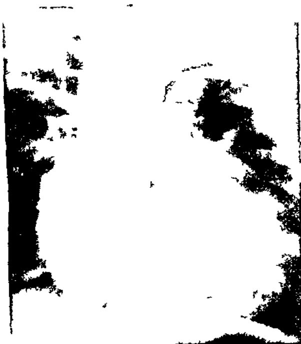


Fig 3 Frontal view of the aortogram showing opacification of the pulmonary arteries.

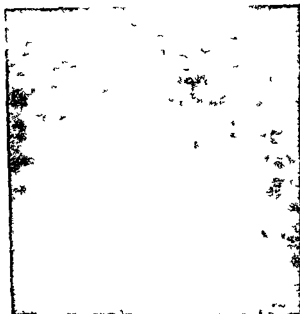


Fig 4 Left oblique view of the aortogram showing the aorticopulmonary septal defect The communication between the two great vessels lies proximal to the origin of the branches of the arch

noses The ECG and roentgenographic findings do not support the diagnosis of corrected transposition of the great vessels The ECG with a frontal plane axis of + 95 degrees also negates consideration of an atrioventricular canal

My clinical impression therefore is ventricular septal defect with congestive cardiac failure An associated patent ductus arteriosus cannot be completely ruled out clinically My primary diagnosis is an intracardiac defect at ventricular level with large left to right shunt Were special studies done?

DR STONE The patient continued to receive digitalis orally and intermittent intramuscular diuretic therapy was added. The dose of digoxin was eventually increased to an equivalent of a total digitalizing dose of 0 09 mg per kilogram In spite of these measures the child remained in chronic congestive cardiac failure The respiratory and cardiac rates remained elevated Cardiomegaly and hepatomegaly persisted. The child continued to feed poorly and did not gain On the fifth day in the hospital further diagnostic studies were carried out in the catheterization laboratory

These various observations dictated certain procedures which along with Dr Kurt Amplatz, I shall describe

No sedation was employed. The catheter was introduced via the right saphenous vein by means of the cutdown technique The essential pressures and oximetry saturations are shown in Table I The catheter tip passed freely from the right atrium to the left atrium and across the mitral valve into the left ventricle Pressure data indicated no gradient across the mitral valve The pressure contours as well as the values for mean pressure were different for the left and the right atria suggesting that the catheter had passed via a patent foramen ovale The blood was fully saturated in the left ventricle and left atrium. A left ventriculogram was performed.

DR KURT AMPLATZ The left ventriculogram revealed a somewhat large left ventricle with a high septal defect The aorta and the pulmonary artery filled simultaneously

DR. STONE. From the right ventricle the catheter was manipulated into the ascending aorta The aortic blood was desaturated (88 per cent) Additionally the peak aortic systolic pressure was not as high as that in the left ventricle

DR AMPLATZ Anteroposterior and lateral views of the aortogram taken with the Schonander rapid film changer revealed immediate opacification of the pulmonary artery A representative anteroposterior view is demonstrated in Fig 3

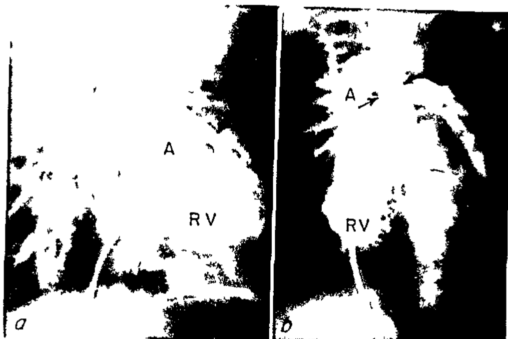


Fig 5 Right ventriculogram a, Right anterior oblique view Simultaneous opacification of the aorta (A) and narrow outflow tract (arrow) of the right ventricle (R V) b Left anterior oblique view The ascending aorta (A.) and the aorticopulmonary septal defect (between arrows) are outlined



Fig 6 Anterior view of base of heart and great vessels In continuity the anterior walls of the aorta (A) the aorticopulmonary septal defect and of the pulmonary trunk (P T) have been removed to show the aorticopulmonary septal defect (between arrows) The branches of the aortic arch lie distal to this zone

Because the aorticopulmonary communication was not demonstrated exactly, the patient was rotated to the left anterior oblique position and a cineaortogram was performed This revealed what appears to be a tubular connection between the aorta and pulmonary artery located in the position of an aorticopulmonary window (Fig 4)

DR STONE The catheter was repositioned in the right ventricle Systolic pressure recorded at that time was the same as that in the aorta There was marked desaturation of right ventricular blood There was concern that the child was acidotic Bicarbonate was administered to correct the acidosis The desaturation in the aorta suggested to us that the intracardiac anatomy was not delineated completely, therefore, a right ventriculogram was taken

DR AMPLATZ With the patient in the left anterior oblique position biplane views were taken The right ventriculogram demonstrates the presence of a hypertrophied infundibular wall and infundibular stenosis There is right to left shunting into the aorta Again, the connection is demonstrated between the ascending aorta and pulmonary artery (Fig 5)

DR STONE The special procedures described were performed over the space of 2 1/2 hours No apparent complications occurred Shortly following the right ventriculogram however a cardiorespiratory arrest occurred No ECG abnormalities had been present on the monitor prior to the development of bradycardia and arrest Rigorous resuscitative attempts were employed but were unsuccessful and the patient died in the catheterization laboratory

Dr Bessinger, will you continue the discussion in the light of these findings?

DR BESSINGER It is apparent from these find

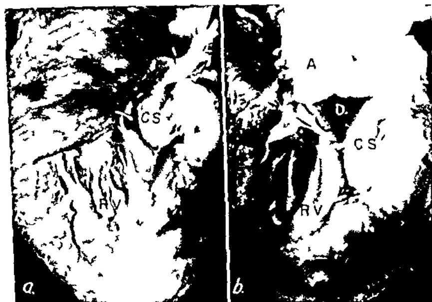


Fig 7 *a*, Interior of right ventricle (R V) showing features characteristic of the tetralogy of Fallot Hypertrophy of wall The subpulmonary outflow tract (probe) is narrow Its posterior wall is formed by an hypertrophied parietal limb of the crista supraventricularis (C S) The latter structure lies anterior to the ventricular septal defect (*D*) *b* Right ventricle (*R V*) and aorta The latter arises in part from the right ventricle above the ventricular septal defect

ings that the problem was not that of a straightforward ventricular septal defect The initial finding of desaturated blood in the aorta is confusing

The aorticopulmonary communication as seen in Fig 4 lies proximal to the position of a patent ductus and, although it runs between the ascending aorta and pulmonary artery it seems atypical of a classic aorticopulmonary window Classically that communication has no length but here it appears to be tubular

The left ventriculogram shows a ventricular septal defect The right ventriculogram shows infundibular stenosis as well as a right to left shunt into the aorta The unequal pressures recorded in the left ventricle and the aorta make us consider the possibility of a double outlet right ventricle with restrictive ventricular septal defect It seems likely (or possible) however that the patient had begun experiencing difficulty and cardiac output was falling at the time that the aortic pressure was recorded and this development may explain the differences in pressures. My postmortem diagnosis therefore is ventricular septal defect with infundibular pulmonary stenosis and, additionally *some type* of aorticopulmonary connection

From the data presented, my final diagnoses are as follows (1) ventricular septal defect (2) infundibular stenosis of the right ventricle (with right to left shunt) and (3) some type of an aorticopulmonary communication (with left to right shunt)

Whether left ventricular outflow obstruction is present additionally cannot be determined as differences in pressures between the two ventricles may reflect differences in cardiovascular status at the times the readings were made

DR STONE. Dr Tandon will you please present the autopsy findings?

DR RAJENDRA TANDON Pathologic findings were confined to the cardiovascular system The heart weighed 45 grams whereas the expected weight in a 3 month old male infant is about 30 grams The abnormal findings consisted of tetralogy of Fallot with aorticopulmonary septal defect and asymmetrical hypertrophy of the ventricular septum resulting in hypertrophic subaortic *stenosis*

Externally the great vessels were normally related. The pulmonary trunk and the aorta were equal in width each measuring 10 mm in external diameter Approximately 5 mm above the pulmonary annulus, the anterior wall of the two great vessels was continuous An aorticopulmonary septal defect, 5 mm in diameter



Fig 8 Left atrium (*LA*) left ventricle (*L V*) and ascending aorta (*A*) Hypertrophy with asymmetrical hypertrophy of the ventricular septum (*VS*) resulting in subaortic stenosis. The probe is through the aortic valve

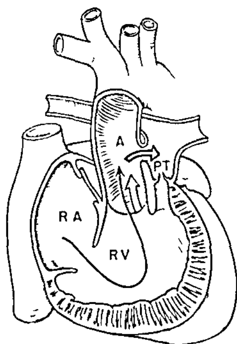


Fig 9 Diagrammatic portrayal of the combination of the tetralogy of Fallot and aorticopulmonary septal defect (horizontal arrow) The subaortic stenosis that is also present is not shown

was located 10 mm above the aortic valve (Fig 6)

The systemic veins and the coronary sinus entered the normal right atrium The foramen ovale was valvular competent and patent The tricuspid valve was normal and led into a markedly hypertrophied right ventricle The wall thickness measured 8 mm The right ventricular outflow tract was narrow, admitting only a 2 mm probe The hypoplastic outflow tract ended in the bicuspid pulmonary valve with a narrow annulus A ventricular septal defect, 5 mm in diameter, was situated posteroinferior to the parietal band of the crista supraventricularis (Fig 7)

The pulmonary venous connections were normal and the left atrium was dilated The endocardium of the left atrium was thickened The mitral valve was normal The left ventricle showed marked hypertrophy of the free walls and asymmetrical hypertrophy of the ventricular septum The free wall was 10 mm thick The asymmetrical hypertrophy of the ventricular septum resulted in marked narrowing of the outflow tract, so called muscular subaortic stenosis The maximum thickness of the ventricular septum measured 17 mm (Fig 8)

The aorta overrode the ventricular septum approximately three fourths arose from the right ventricle and one fourth from the left ventricle The aortic valve had three cusps and the coronary arteries came off behind the right and left cusps The aortic valve–mitral valve continuity was present. The aortic arch was to the left. The ductus arteriosus was absent

In summary, this patient had an aorticopulmonary septal defect with a ventricular septal defect and hypoplastic right ventricular outflow tract as seen in tetralogy of Fallot In addition, asymmetrical hypertrophy of the ventricular septum had resulted in muscular subaortic stenosis Diagrammatic portrayal of the anomaly is presented in Fig 9

DR JESSE E EDWARDS This case combines the rare anomaly of aorticopulmonary septal defect with tetralogy of Fallot as well as subaortic stenosis resulting from asymmetrical hypertrophy of the ventricular septum Embryologically aorticopulmonary septal defect has been considered to be "partial persistent truncus arteriosus

Neufeld and associates[2] collected 66 cases of aorticopulmonary septal defect 60 of which were

from the literature Their analysis indicated that aorticopulmonary septal defect was uncommonly associated with other anomalies The commonest associated anomaly was patent ductus arteriosus which was seen in eight of 66 cases (12 per cent) of aorticopulmonary septal defect Less common associated anomalies were coarctation of the aorta (three cases) and a right aortic arch (two cases) Other anomalies occurred in isolated instances Tetralogy of Fallot was noted once[3] and membranous subaortic stenosis in another case[4] As far as we are aware the case under discussion is the second reported case of aorticopulmonary septal defect associated with tetralogy of Fallot and the first in which subaortic stenosis due to asymmetrical hypertrophy of the ventricular septum was seen in association with aorticopulmonary septal defect Morrow and associates[5] reported on six patients with aorticopulmonary septal defect, in one of whom (case 3) subaortic stenosis was present however the exact anatomic basis of the subaortic stenosis in their case is not known

The presence of ventricular septal defect in association with aorticopulmonary septal defect has been reported in a number of cases[3,6,9] In one of these[3] it was part of tetralogy of Fallot as in this case It seems unusual that, while persistent truncus arteriosus is always associated with a ventricular septal defect aorticopulmonary septal defect is only rarely so associated.

Another interesting feature was absence of the ductus arteriosus in the case presented. This state may be seen in association with persistent truncus arteriosus aorticopulmonary septal defect, and the tetralogy of Fallot.

Its absence may be explained by ready communication of the right ventricle with the aorta in each of these conditions Perhaps favored flow through a route other than the ductus arteriosus is responsible for early atrophy of the left sixth aortic arch with resulting loss in its identity

The fundamental hemodynamics in the patient presented were like those in the tetralogy of Fallot following surgical creation of a Waterston type of aorticopulmonary anastomosis The resulting large left to right shunt is considered responsible for absence of cyanosis and development of left ventricular failure These in turn masked the usual features of the tetralogy of Fallot Left ventricular failure is probably compounded of the left to right shunt through the aorticopulmonary septal defect and the subaortic stenosis[5]

FINAL DIAGNOSIS Tetralogy of Fallot with aorticopulmonary septal defect and muscular subaortic stenosis

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Hypertension and anxiety

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There is clinical and laboratory evidence that emotional stress may cause transient elevations of blood pressure Graham[1] found that 25 per cent of soldiers with long combat experience developed hypertension for several months afterward and Ruskin and colleagues[2] observed that 57 per cent of the victims of the Texas City nitrate explosion were hypertensive for two weeks after the event Funkenstein and his group[3] studied the cardiovascular responses to anxiety and anger They observed increased blood pressure stroke volume, heart rate and cardiac output with anger and anxiety and reduced peripheral resistance with the latter Welch and Welch[4] found marked enlargement of the adrenal glands and increased adrenal medullary catecholamines in mice exposed to brief daily stress for 10 to 15 days, and Forsyth and Harris[5] achieved a sustained elevation of systolic blood pressure in rhesus monkeys exposed to psychological stimuli Folkow and Rubinstein [6] upon stimulation of the hypothalamic defense area in rats induced an alerting response which was accompanied by increases in blood pressure heart rate, and muscle blood flow

Epinephrine (E) has been found to induce anxiety when administered to human subjects and Basowitz and co workers[7] reported that normal persons during E infusion experienced feelings similar to those felt in previous spontaneously occurring anxiety attacks Since we were already testing patients for increased reactivity to norepinephrine (NE) we decided to test their responsiveness at the same session to E as well because E is a natural substance believed to be secreted during anxiety states [8] In another communication [9] the results of E as well as of NE infusion during ganglion blockade in 33 hypertensive and 13 normotensive subjects were reported Four grades of susceptibility to anxiety were established in these subjects on the basis of clinical criteria While there was low correlation between the grade of susceptibility to anxiety and the responses of systemic blood pr ssure and heart rate to infusion of E there was surprisingly good correlation between this grading and the digital vascular reactivity to E When the hypertensives as a whole were compared with the normotensives as a whole reactivity to E was significantly greater in the hypertensive group ($p < 0.005$) In the present study formal psychological tests were administered to evaluate characterologic anxiety and overt affective responses to E infusion in both hypertensive and normotensive subjects The results of the psychological testing were then correlated with the digital vascular reactivity to E and NE as well as with the heart rate and brachial blood pressure changes during E infusion

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Methods

Studies were carried out in 13 normal volunteers and in 22 essential hypertensive patients most of whom had labile fluctuations of blood pressure In all subjects medication was with

Table I Clinical data in the hypertensive and normotensive groups

Group	*Number of cases*	*Mean age (yr)*	*Sex*	*Race*	*Family history of hypertension*	*Type of hypertension*
A	22	45 6	12 M 10 F	16 C 4 N 2 PR	19 + 3 −	11 L 11 S
B	13	26 3	10 M 3 F	8 C 3 N 2 PR	9 + 4 −	

Abbreviations and symbols A = hypertensive B = normotensive M = male F = female + = positive − = negative L = labile S = sustained, C = Caucasian N = Negro PR = Puerto Rican

drawn for at least two weeks prior to testing Routine investigation consisted of history physical examination and laboratory procedures including hemogram urinalysis 6 and 12 channel automated blood chemistry urinary catecholamine metabolite assay and in some cases 24 hour urinary electrolyte concentration Chest x ray electrocardiogram rapid sequence intravenous pyelogram and protein bound iodine determination were also carried out Patients with coronary artery disease cardiac arrhythmias cerebrovascular disease thyroid disorders and renal failure were excluded.

Each subject was interviewed in the laboratory during the first minutes of his arrival by the same investigator under similar environmental conditions He or she was then requested to complete the Institute for Personality and Ability Testing (IPAT) anxiety scale developed by Cattell[10]

The IPAT anxiety scale which has been validated extensively in psychophysiologic studies provides a measure of personality trait anxiety It is a reliable self administered test consisting of 40 questions designed to assess overt as well as covert anxiety related to various personality characteristics. The patient was then put to bed and blood pressure and heart rate were recorded both before and 30 minutes after relaxation Then the digital vascular reactivity (DVR) to E and NE was carried out in four phases The Manifest Affect Rating Scale of Jacobs[11] (MARS) was employed immediately prior to and at the completion of the E infusion (Phase C) for the assessment of overt emotions in the following categories anxiety hostility depression combined unpleasant affect and pleasurable affect This test which is based on the subject s response to a list of 87 specific questions is administered in ten minutes and can be used repeatedly to measure both momentary states as well as rapid shifts of affect

The four phases of the physiological procedure were carried out as follows

Phase A Thirty minutes of complete relaxation with the room temperature between 26 and 29° C

Phase B After vasodilation was produced by indirect heating with electric blankets until positive heat balance manifested by profuse perspiration was attained a ganglion blocking agent trimethaphan camphorsulfonate (TMCS) in a solution of 5 per cent dextrose in water was then infused at a dosage of 0 5 to 0 8 mg per minute for 15 to 20 minutes until the brachial blood pressure was stabilized at a level 20 to 40 mm Hg below the resting blood pressure

Phase C Keeping the conditions in phase B constant the infusion was replaced by another one containing (E) (epinephrine chloride) in addition to TMCS and was given for 15 to 17 minutes at a rate of 0 1 μg E per kilogram of body weight per minute

Phase D Keeping the conditions in phase B constant and 30 minutes after the end of phase C an infusion of levarterenol bitartrate 3 mg NE base in 250 ml 5 per cent dextrose solution in addition to TMCS was given for 15 to 17

Table II Hypertensive group

	IPAT* Test (Sten scores)	Mean BP (mm. Hg)		Heart rate (beats/min)		DVR to		ANESR
		I	R	I	R	E	NE	
Range	4 to 10	89 to 150	92 to 147	72 to 124	68 to 112	−2 to +605	0 to +571	13 to 59
Mean	6 9	127	124	95	88	+163	+143	35
S D	±1 5	±17	±14	±15	±14	±148	±115	±12
p		<0 05		<0 001				

Abbreviations IPAT = Institute for Personality and Ability Testing E = epinephrine NE = norepinephrine ANESR = apparent norepinephrine secretion rate B P = blood pressure DVR = digital vascular reactivity I = initial R = resting S D = standard deviation p = probability (paired t test)

Table III Hypertensive group

	MARS Test Scores										Circulatory changes during E infusion		
	Pleasant		Depression		Anxiety		Hostility		Unpleasant				
	A*	B	A	B	A	B	A	B	A	B	HR	SBP	DBP
Range	23 to 79	15 to 90	0 to 56	0 to 43	0 to 79	0 to 79	0 to 42	0 to 50	0 to 50	6 to 45	0 to +32	−5 to +50	−38 to +5
Mean	53	51	13	14 5	17	34	8	9 8	13	20	+12	+17	−14
S D	±17	±19	±14 5	±13	±20	±23	±14	±12 6	±15	±13	±8 9	±12	±9 8
p	ns		ns		<0 005		ns		<0 005		<0 001	<0 001	<0 001

Abbreviations and symbols A = before E infusion B = during E infusion HR = heart rate SBP = systolic blood pressure DBP = diastolic blood pressure S D = Standard Deviation p = probability (paired t test) ns = not significant

minutes at a rate of 6 to 9 μg NE base per minute The intravenous flow rate was kept the same as in previous phases unless an excessive response of the blood pressure necessitated a lower flow rate

In all four phases the digital blood flows (calorimetric) and digital blood pressures (flush throb) were measured and the radius equivalents were determined The work of vasoconstriction based upon the E and NE infusion rate was then calculated and expressed in ergs per μg of infused E or NE per minute [12] In addition, brachial cuff blood pressures and heart rates were recorded just before and at the end of each phase The entire procedure lasted approximately two and one half hours

On a subsequent day in all the normotensive, and in 20 of the hypertensive subjects the apparent NE secretion rate (ANESR) was measured as follows 6 2 μg (500 μCi) of DL beta tritiated NE was injected intravenously over a period of three minutes following which 24 hour

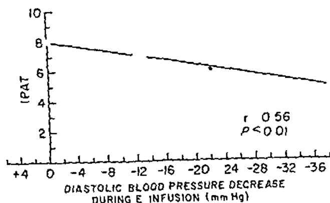


Fig 1 Hypertensive group Correlation between degree of diastolic blood pressure decrease during epinephrine (E) infusion and chronic anxiety as measured by the *IPAT*

urine was collected. The specific activity of nor metanephrine (NM) was measured in an aliquot. The ANESR represented the counts of tritium given divided by the specific activity of NM [13]

Results

The clinical data in the hypertensive group are presented in Table I The mean age in the hypertensive group was 45 6 years and the male to female ratio was 1 2 At least half of the hy pertensive patients had labile hypertension as suggested by normal resting blood pressures and by the history The mean blood pressures and heart rates after resting were significantly lower than initially (Table II) No significant correla tion was found between personality trait anx iety as measured by the IPAT test and the ini tial or resting brachial blood pressure the initial or resting heart rate or their degree of change Correlations between IPAT anxiety scores and DVR to E or to NE as well as between such scor ing and changes of heart rate or systolic blood pressure during the infusion of E were also not statistically significant. A significant negative correlation however between IPAT anxiety scores and diastolic blood pressure decrease was found during the E infusion (r = 0 56 p < 0 01) (Fig 1)

The range and mean values of overt affect in the hypertensive group as measured by the MARS test before and during E infusion are pre sented in Table III Epinephrine infusion resulted in a significant increase in anxiety and combined unpleasant affect scores with no sig nificant change in depression hostility and pleasurable affect. There was no significant cor relation between the change in anxiety scores and brachial blood pressure or heart rate change during E infusion although the changes in these measurements during E infusion were statistically significant The DVR to E was not significantly related to the affective response measured before infusion Epinephrine infusion however resulted in a significant positive cor relation between DVR to E and degree of anxiety (Fig 2) as well as combined unpleasant affect assessed during the infusion (Fig 3)

Low correlation was also found between DVR to E and blood pressure or heart rate change during infusion of E The DVR to NE was abnor mal in only five of the 22 hypertensive subjects and the ANESR was abnormal in only three of the 20 hypertensive subjects tested. While the correlation between the extent of abnormality in the DVR to NE and the extent of abnormality in the ANESR was low (r = 0 41) in only one case was there a discrepancy between the two tests as to whether they were within the normal range or definitely abnormal A significant positive cor relation was found between DVR to E and DVR to NE (Fig 4) while there was no significant cor relation between DVR to E and ANESR

In the normotensive group the mean age was 26 3 and male to female ratio was 3 3 (Table I) In all normotensive subjects both DVR to NE and ANESR were within normal limits (Table IV) Here as in the hypertensive group there was no significant correlation between the anx iety scoring in the IPAT test and DVR to E or NE A significant positive correlation however was found between the IPAT anxiety scores and the decrease in diastolic pressure during E infu

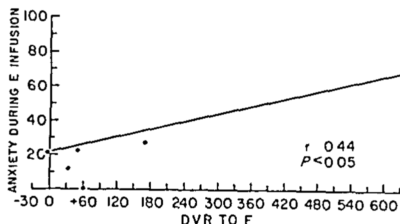


Fig 2 Hypertensive group Correlation between digital vascular reactivity *(DVR)* to epinephrine *(E)* and anxiety during F infusion as measured by the MARS test

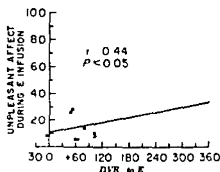


Fig 3 Hypertensive group Correlation between digital vascular reactivity *(DVR)* to epinephrine *(E)* and unpleasant affect during E infusion

sion (Fig 5) This correlation contrasts with the corresponding negative correlation in the hypertensive group

The range and mean values for the overt affects measured by the MARS test before and during the infusion of E in the normotensive group are presented in Table V As with the hypertensive group are presented in Table V As with the hypertensive group epinephrine infusion resulted in a significant increase in anxiety and total unpleasant affect scores (Table III and V) In addition a decrease in pleasant affect score was also observed in the normotensive group There was no relation between overt affect before or during E administration and the degree of change in blood pressure or heart rate during infusion In contrast to the hypertensive group, there was also no correlation between DVR to E and the overt affective responses to infusion

Although the DVR to E was significantly greater in the hypertensive than in the normotensive group (Table VI), the scoring for personality trait' anxiety as well as for temporary anxiety did not differ significantly between the two groups of subjects (Table VII) While the DVR to E in the group of hypertensives with normal DVR to NE was higher than in the normotensive group anxiety scoring during E infusion was not significantly different in the two groups (Table VIII) The DVR to NE of the hypertensive subjects did not differ significantly from the normotensives (Table VI), probably because of the small number of such hypertensive subjects

Discussion

Although the diagnosis of essential hypertension is usually made by excluding secondary causes of the disease Mendlowitz and associates[14] have observed a striking and uniform increase of DVR to NE in established essential hypertension This is usually a very early phenomenon and similar increases in reactivity may be found in the prehypertensive [15] Wolf and associates[13] reported that single injections of tritiated NE resulted in a decreased apparent NE secretion rate in essential hypertension The same workers[16] found that the secretion rate was normal in many patients with renal and renovascular hypertension Gitlow and coworkers [17] who were evaluating NE metabolism by administering various doses of ^{3}H NE in a single intravenous injection found that at a dose of 8 μg (200 μ Ci) of ^{3}H NE the urinary excretion of tritium was greater in patients with essential hypertension than normal Again many of the renovascular and renal hypertensive patients fell into the normal range In the present study all the normotensive subjects had normal DVRs to NE and normal ANESR with a good correlation between both tests (r = 0 63 p < 0 05) In the hypertensive group 17 out of 22 patients had

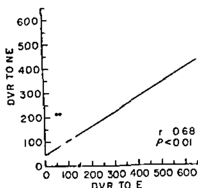


Fig 4 Hypertensive group Correlation between digital vascular reactivity *(DVR)* to epinephrine *(E)* and norepinephrine *(NE)*

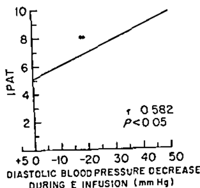


Fig 5 Normotensive group Correlation between degree of diastolic blood pressure decrease during epinephrine *(E)* infusion and chronic anxiety as measured by the *IPAT*

normal DVR to NE and 17 out of 20 had normal ANESR Since all specific tests for secondary causes of hypertension were negative there seemed to be no objective factor related to the hypertension of these patients Suck and colleagues[18] described a group of labile hypertensive patients in whom DVR to NE ANESR and tritiated NE uptake were normal and self determined home blood pressures were also normal It was suggested that these hypertensive patients developed sporadic hypertension because of anxiety and that this condition could in some cases be superimposed on established essential hypertension In our hypertensive group at least 11 of the patients had labile hypertension and two of the five hypertensive patients with abnormal DVR to NE also had labile blood pressures

The findings of this study show that hypertensive and normotensive subjects did not differ in the levels of anxiety measured by the IPAT test and in overt affected determined prior to E administration Infusion of E resulted in a significant increase in anxiety and total unpleasant affect of a similar magnitude in both groups

In the hypertensive group a significant correlation between DVR to E and anxiety as well as unpleasantness during E infusion was found (both $p < 0.05$) whereas such a correlation was not found in the normotensive group In both groups of subjects a significant correlation was observed between chronic anxiety and changes in diastolic blood pressure during E infusion but in a different direction for normotensive as against hypertensive subjects. It is obvious from the data that while the hypertensive subjects did not score higher for personality trait anxiety than the normotensive group they demonstrated a statistically higher DVR to E which was well correlated with reactive anxiety and total unpleasant emotion during E infusion In the hypertensive group however the diastolic blood pressure decreased less in the more anxious subjects and this was opposite to the changes in diastolic blood pressure in the normotensive group Similar results were reported in another study[9] In the present as well as in the other study a good correlation between DVR to E and DVR to NE was observed in the hypertensive group only (Fig 4)

From the above data it is reasonable to conclude that these hypertensive subjects many of whom had labile blood pressures had abnormal circulatory responses under stress manifested by higher DVR to E at a statistically significant level ($p < 0.02$) Malmo[19] demonstrated that when individuals with various psychosomatic complaints are subjected to stress they are most likely to respond maximally with disturbances in the critical symptom area —i e the area in which the psychosomatic complaint was related. A striking example of autonomic response specificity was reported by Engel and Bickford[20] They subjected 20 female hypertensive and 20 matched normotensive subjects to five stimuli while making measurements of physiological responses They did not find any difference in the frequency of occurrence of individual specific response between the two groups but 15 of the hypertensive subjects had their greatest degree of response in blood pressure while only five of the normotensive did In the present study while the DVR to NE be ween the two groups

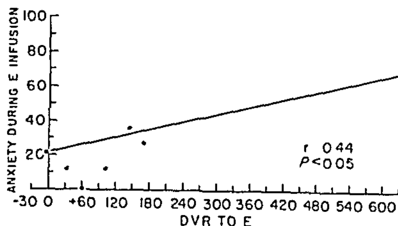


Fig 2 Hypertensive group Correlation between digital vascular reactivity *(DVR)* to epinephrine *(E)* and anxiety during E infusion as measured by the MARS test

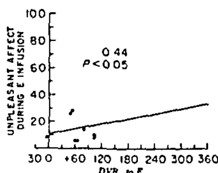


Fig 3 Hypertensive group Correlation between digital vascular reactivity *(DVR)* to epinephrine *(F)* and unpleasant affect during E infusion

sion (Fig 5) This correlation contrasts with the corresponding negative correlation in the hyper tensive group

The range and mean values for the overt affects measured by the MARS test before and during the infusion of E in the normotensive group are presented in Table V As with the hy pertensive group are presented in Table V As with the hypertensive group epinephrine infu sion resulted in a significant increase in anxiety and total unpleasant affect scores (Table III and V) In addition, a decrease in pleasant affect score was also observed in the normotensive group There was no relation between overt af fect before or during E administration and the degree of change in blood pressure or heart rate during infusion In contrast to the hypertensive group, there was also no correlation between DVR to E and the overt affective responses to in fusion

Although the DVR to E was significantly greater in the hypertensive than in the nor motensive group (Table VI), the scoring for per sonality trait anxiety as well as for temporary anxiety did not differ significantly between the two groups of subjects (Table VII) While the DVR to E in the group of hypertensives with normal DVR to NE was higher than in the nor motensive group anxiety scoring during E infu sion was not significantly different in the two groups (Table VIII) The DVR to NE of the hy pertensive subjects did not differ significantly from the normotensives (Table VI) probably because of the small number of such hyperten sive subjects

Discussion

Although the diagnosis of essential hyperten sion is usually made by excluding secondary causes of the disease Mendlowitz and associ ates[14] have observed a striking and uniform in crease of DVR to NE in established essential hy pertension This is usually a very early phenomenon, and similar increases in reactivity may be found in the prehypertensive [15] Wolf and associates[13] reported that single injections of tri tiated NE resulted in a decreased ' apparent NE secretion rate in essential hypertension The same workers[16] found that the secretion rate was normal in many patients with renal and renovascular hypertension Gitlow and co workers [17] who were evaluating NE metabolism by administering various doses of ^{3}H NE in a single intravenous injection found that at a dose of 8 μg (200 μ Ci) of ^{3}H NE the urinary excre tion of tritium was greater in patients with es sential hypertension than normal Again many of the renovascular and renal hypertensive pa tients fell into the normal range In the present study, all the normotensive subjects had normal DVRs to NE and normal *ANESR* with a good cor relation between both tests ($r = 0.63$ $p < 0.05$) In the hypertensive group 17 out of 22 patients had

Table VII Anxiety levels in hypertensive and normotensive subjects

	Number of cases	IPAT Test			MARS Test					
					Before E			During E		
		Mean	S.D	p	Mean	S D	p	Mean	S D	p
Hypertensive	22	6 9	±1 5		17	±20		34	±23	
versus				ns			ns			ns
Normotensive	13	7	±1 9		16	±15		43	±23	

Abbreviations and symbols same as in previous tables.

Table VIII Digital vascular reactivity to epinephrine (E) and anxiety during epinephrine (E) infusion in hypertensive subgroups and normotensive subjects

Group	Number of cases	DVR† to E			Anxiety during E infusion		
		Mean	S D	p	Mean	S D	p
A	5	258	±204		48	±10	
versus				ns			ns
B	17	135	± 88		29 7	±23	
versus				<0 1			ns
C	13	75	± 77		42 5	±20	
versus				ns			ns
A	5	258	±204		48	±10	

A = hypertensive subgroup with abnormal DVR to NE B = hypertensive subgroup with normal DVR to NE C = normotensive subjects
†Other symbols same as in Table II

of subjects did not differ significantly the differences in DVR to E were significant The blood pressure and heart rate changes during E infusion however did not differ significantly between the hypertensives and the normotensives. In the subgroup of 17 hypertensive subjects with normal DVR to NE, the DVR to E was also higher than in the normotensive but this was significant only at the p < 0 1 level It was, however more significant in another study of a larger group[9]

It is apparent that there is little evidence for characterologic anxiety as such in the hypertensive group studied, at least as measured by the IPAT test Since many questions in this test are ideational defensive answers might alter some scores whereas questions with reference to reactions to stress[9] might elicit less defensive

Table IV Normotensive group

	IPAT* Test (Sten scores)	Mean BP (mm Hg)		Heart rate (beats/min)		DVR to		ANESR
		I	R	I	R	E	NE	
Range	4 to 10	77 to 107	74 to 107	52 to 100	52 to 102	8 to 241	20 to 170	33 to 60
Mean	7	94	89	80	77	75	97	45 7
SD	±1 9	±9 7	±11	±14	±14	±77	±37 5	±7 7
p		<0 005		ns				

Abbreviations and symbols same as in Table II

Table V Normotensive group

	MARS Test Scores										Circulatory changes during E infusion		
	Pleasant		Depression		Anxiety		Hostility		Unpleasant				
	A*	B	A	B	A	B	A	B	A	B	HR	SBP	DBP
Range	42 to 81	28 to 74	0 to 29	0 to 31	0 to 44	9 to 88	0 to 33	0 to 61	1 to 35	5 to 55	+4 to +36	+7 to +35	-43 to +5
Mean	60	50	7	11	16	43	7	13	10	23	+15	+21	-20
SD	±12	±16	±9	±9	±15	±20	±11	±18	±11	±13	±11	±9 5	±13
p	<0 05		ns		<0 005		ns		<0 025		<0 001	<0 001	<0 001

Abbreviations and symbols same as in Table III

Table VI Digital vascular reactivity in hypertensive and normotensive subjects

	Number of subjects	DVR to E			DVR to NE		
		Mean	SD	p	Mean	SD	p
Hypertensive	22	162 8	±147 8		143 5	±115	
versus				<0 02			ns
Normotensive	13	74 9	±76 8		96	±37 5	

Abbreviations and symbols as in previous tables

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responses These patients do, however, react correlatively to stimuli psychologically and physiologically (DVR to E) The curious paradoxical correlations between IPAT anxiety scoring and the diastolic blood pressure decrease with E infusion in the normotensive versus the hypertensive group remain unexplained unless it is postulated that anxiety produces more vasoconstriction than increase in cardiac output in the hypertensive, whereas the opposite obtains in the normotensive subject

Summary

1 Epinephrine (E) as well as norepinephrine (NE) was infused during ganglion blockade in 22 hypertensive and 13 normotensive subjects and circulatory responses including digital vascular reactivity (DVR) were recorded The apparent NE secretion rate (ANESR) was also measured in most of the subjects

2 The hypertensive group included many patients with labile as well as with established essential hypertension

3 Formal psychological tests were administered to evaluate personality ' trait anxiety (IPAT test) as well as to assess both momentary affect and rapid shifts of overt emotions in the following categories pleasurable affect depression anxiety hostility, and combined unpleasant affect (MARS test)

4 No significant correlation was found between IPAT anxiety scores and DVR to E or NE initial or resting blood pressure initial or resting heart rate or between such scoring and changes in blood pressure or heart rate during E infusion, in both normotensive and hypertensive groups Correlation was significant between anxiety scores and diastolic blood pressure decrease during E infusion but in a different direction for normotensive as against hypertensive subjects

5 Epinephrine infusion induced a significant increase in anxiety and combined unpleasant affect of a similar magnitude in normotensive and hypertensive subjects

6 In the hypertensive group correlation between DVR to E and anxiety as well as unpleasant affect during E infusion was significant, whereas such correlation was not significant in the normotensive group

7 Although scoring for personality trait anxiety was no higher in the hypertensive than in the normotensive group, DVR to E was significantly higher in the hypertensive group

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INDEX TO ADVERTISERS

While every precaution is taken to insure accuracy we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index

Physiologic basis for the therapeutic use of catecholamines

Robert Rosenblum M D
New York N Y

In an attempt to reverse the morbid effects of hypotension shock syndrome associated with myocardial infarction (MI) or low cardiac output accompanying severe congestive heart failure (CHF) catecholamines are the major medical therapeutic approach

The commonly used agents norepinephrine epinephrine isoproterenol and dopamine all have the common property of stimulating cardiac contractility and therefore increase cardiac output but the action of these drugs on heart rate renal blood flow and peripheral vascular resistances differ It is a review of their common properties and their differences that is the basis of this report Table I summarizes the physiologic effects of catecholamines administered intravenously to an intact animal or man All catecholamines must be given intravenously as they are destroyed in the gastrointestinal tract.

Clinical pharmacodynamics

Cardiac output All four catecholamines increase the contractility of the heart by direct stimulation of the β receptor sites in the myocardium Therefore the cardiac output is increased by augmenting stroke volume Isoproterenol the most potent inotropic agent increases cardiac output by an increase in heart rate as well as stroke volume In addition the isoproterenol stimulated heart contracts against a decreased afterload.

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Heart rate All catecholamines stimulate the β receptor sites and therefore may have a positive myocardial chronotropic action The administration of norepinephrine can result in a reflex bradycardia due to baroreceptor stimulation when blood pressure rises Epinephrine increases heart rate due to its more potent β adrenergic chronotropic effect compared with norepinephrine Isoproterenol the most potent β stimulator has the greatest positive chronotropic action of all the catecholamines It often produces tachyarrhythmia or abnormal rhythms limiting its use Dopamine can increase cardiac output without increasing heart rate However large concentrations of the drug may increase the rate and/or produce aberrant rhythms These toxic effects occur far less frequently than with the use of isoproterenol or epinephrine

Renal blood flow Norepinephrine by stimulation of α receptor sites increases peripheral vascular resistance Therefore the renal vascular resistance is increased with a resultant decrease in renal blood flow and glomerular filtration rate Epinephrine also decreases renal blood flow and glomerular filtration rate Isoproterenol, despite its ability to increase muscle and skin blood flow does not significantly affect renal blood flow or glomerular filtration rate in the nonshock state

Dopamine is the only catecholamine that specifically increases renal blood flow and glomerular filtration rate by decreasing renal vascular resistance The exact mechanism remains unknown In very high concentrations usually greater than 50 μg per kilogram of body weight per minute renal vasoconstriction may occur

Cerebral blood flow None of the catecholamines primarily affect the cerebral vasculature All increase in cerebral blood is secondary to the

output and their ability to alter the peripheral vascular resistance Norepinephrine is the most potent agent in raising blood pressure It increases peripheral resistance and also increases cardiac output Therefore both systolic and diastolic blood pressures are increased Epinephrine quantitatively effects blood pressure as does norepinephrine but is not as potent Isoproterenol elevates systolic pressure whereas the diastolic pressure decreases or remains unchanged. This is the result of an increase in cardiac output associated with a decrease in peripheral vascular resistance Dopamine may increase systolic blood pressure because it increases stroke volume The increase in cardiac outputs results in a reflex vasodilation and, therefore the diastolic pressure remains unchanged or decreases In large concentrations greater than 40 to 50 μg per kilogram of body weight per minute its peripheral actions are similar to norepinephrine—augmenting systolic and diastolic systemic pressures

These pharmacodynamic effects are based on studies in normotensive man and animals Therefore the clinical observations of the actions of catecholamines in shock may at times differ

Clinical application

In low cardiac output states or shock when there is inadequate perfusion or inadequate pressure to perfuse vital organs any pharmacologic agent that augments cardiac output and/or increases systemic blood pressure will increase at least transiently blood flow to all vital structures However under these circumstances the increased blood flow and therefore functions of such organs as the kidney brain heart splanchnic bed etc may not reflect the physiologic actions of the drug on a given organ system

Shock associated with acute MI

It has been demonstrated that shock associated with acute MI depends upon the amount of muscle mass that has been destroyed at the time of the onslaught. However there are certain areas of ischemic muscle that may recover if adequate coronary perfusion can be maintained. Whether this ischemic tissue can function will often determine whether the patient will survive the shock state Ideally the medical management of myocardial shock will require a drug that maintains blood pressure increases cardiac output without change in heart rate and dilates the coronary arteries Norepinephrine does not exhibit all these properties but is the drug of choice in the treatment of myocardial shock Dopamine which has a similar action to norepinephrine but a less potent α stimulating effect on the peripheral vasculature would be a second line agent However in MI associated with severe CHF dopamine because of its unique effect on renal blood flow would be the agent of choice with norepinephrine as the secondary catecholamine to be used. Epinephrine s actions are similar to norepinephrine but often increases heart rate or produces aberrant rhythms Isoproterenol is not a first line agent in myocardial shock because of its potent chronotropic effect and its beta effect on the peripheral vasculature decreasing diastolic blood pressure and, therefore possibly decreasing coronary perfusion In addition the potent inotropic and chronotropic actions of isoproterenol increase myocardial oxygen needs more than the other catecholamines

Low cardiac output syndrome after open heart surgery

After open heart surgery for correction of mechanical defects, be it valvular or bypassing obstructed coronary arteries cardiac action may not allow adequate perfusion of vital organs Isoproterenol and epinephrine have been used successfully under these conditions Both agents increase cardiac output by increasing myocardial contractility and heart rate Increasing cardiac output and maintaining adequate blood pressure the renal vascular bed receives an increased blood supply and, therefore is able to excrete more sodium and water However these two agents particularly isoproterenol have a potent chronotropic action and often produce tachycardia and/or arrhythmias These complications often perclude the use of these drugs Dopamine has been shown theoretically and in clinical trials to increase the cardiac output and at the same time to increase the excretion of salt and water This agent has less chronotropic action and produces arrhythmia less frequently than isoproterenol or epinephrine This unique combination makes dopamine the drug of choice in the treatment of low cardiac output syndrome after open heart surgery

Table 1 Physiologic effects of catecholamines in animal or man

	Dopamine	*Norepinephrine*	*Epinephrine*	*Isoproternol*
Chemical structure	HO ⬡ $CH_2CH_2NH_2$ OH	HO ⬡ $CH(OH)CH_2NH_2$ OH	HO CH(OH)CH_2 OH $NH(CH_3)$	HO ⬡ CH(OH)CH_2NH OH $CH(CH_3)_2$
Cardiac output	Increase	Increase	Increase	Increase
Stroke volume	Increase	Increase	Increase	Increase
Heart rate	No change or increase	No change or decrease	Increase	Increase
Coronary blood flow	Increase	Increase	Increase	Increase
Renal blood flow	Increase	Decrease	Decrease	No change
Cerebral blood flow	Increase	Increase	Increase	Increase
Splanchnic blood flow	Increase	Decrease	Decrease	Increase
Muscular blood flow	Increase or decrease†	Decrease	Decrease	Increase
Skin blood flow	Increase or decrease†	Decrease	Decrease	Increase

Normal coronary arteries
†Dose related

increase in cardiac output This is of little importance in normotensive patients but of great importance in patients with shock or with markedly depressed cardiac output due to severe myocardial dysfunction

Coronary blood flow The net effect of catecholamines ability to increase oxygen in the myocardium depends upon the net balance of these drugs to increase myocardial oxygen utilization by their actions of increasing myocardial contractility and heart rate versus their ability to increase myocardial blood flow by augmenting cardiac output and decreasing coronary vascular resistance

Oxygen requirement of the myocardium is the most important factor in controlling coronary blood flow Therefore the direct action of a pharmacologic agent on the coronary vasculature gives little clue to its net effect on myocardial blood flow In animal studies norepinephrine, epinephrine, and dopamine when infused directly into the coronary arteries causes vasoconstriction As the inotropic action of these catecholamines increases myocardial oxygen consumption, a vasodilation of the coronary arteries occurs with a resultant increase in coronary blood flow Despite this reflex vasodilation, myocardial oxygen utilization may exceed increased oxygen delivered Isoproterenol dilates normal coronary arteries either when infused directly into the coronary arteries or given intravenously to man or animal In atherosclerotic vessels the ability of isoproterenol to dilate the vessels is minimal whereas its potent inotropic and chronotropic effect may result in a significant increase in myocardial oxyger utilization the net effect is often a myocardial oxygen debt

Splanchnic blood flow In man the vascular tone of the intestine liver, pancreas etc is under the same receptor control as the muscle and skin vessels Norepinephrine and epinephrine, both potent stimulators of the α receptor sites in the peripheral vasculature will decrease flow to the gastrointestinal organs by vasoconstricting these vessels. Isoproterenol will vasodilate these vessels by direct β stimulation Therefore the gut will receive an increased blood flow This latter effect is blocked by propranolol Dopamine increases blood flow through the gastrointestinal area but this effect is not blocked by β blocking agents and is probably mediated by the same mechanism that causes dopamine to increase renal blood flow Haloperidol will block dopamine s ability to vasodilate the renal and mesenteric vessels

Blood pressure The numerical number obtained either directly or indirectly from a peripheral artery is the net effect of (1) the effectiveness of the pump (the heart) (2) the resistance of the vessels through which the blood must flow, and (3) the volume of fluid circulating in the system

In this review altered volume states are not considered therefore the effect of catecholamines on blood pressure in the nonshock state will depend upon their ability to increase cardiac

Annotations

Of thinking

The opportunity to think is the privilege of all people This silent process can be denied no one Unfortunately too few people think seriously critically and creatively To think productively requires time knowledge, a healthy brain, and the ability and desire to do so Creative thinking is limited to extremely few people This type of thinking is most satisfying pleasurable and exciting Some of the most complex research and investigations can be conducted in the mind without physical effort. With careful preliminary thinking wasting of many hours of laboratory research and physical effort is avoided. And, with careful creative thinking the experiments in the laboratory become simple and the results clearly defined, the answers and findings often merely confirming the data already obtained by thought.

Nevertheless there is a great need for careful productive and creative thinking Most of the actions of man are expressions of errors, lack of adequate thought Mankind would be considerably more advanced today were thinking better more critical, and more extensive Furthermore to sit or lie and think is a great pleasurable hobby Planning of activities and studies well in advance is pleasant and is necessary if efficient performance is to follow Unfortunately the educational systems are not adequately designed to teach and motivate people to think Apparently creative thinking can be learned by working with one who thinks

The factors required for creative thinking are too numerous to list. However the field or problems or questions to ask must first be known Too many people know not what questions to ask or what to think about Good health of brain and body is necessary But the knack or ability to think creatively is possessed by few people Those who can should think extensively and others should think at least a little

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Diagnosis of transient arrhythmias

When effective therapy is available for an illness accurate and prompt diagnosis assume extreme importance

In recent years a great deal has been learned of cardiac arrhythmias and of their management. In the context of the patient with a recent myocardial infarct their detection and prompt management have saved many lives which would have been lost in the days when their importance passed unrecognized and when in any case little was known of efficient therapy However cardiac arrhythmias of a transient nature do present themselves in other situations and with varied symptomatology They may just produce an unpleasant feeling of palpitations" and have no other sinister manifestations. In patients whose coronary circulation is already compromised by atheromatous narrowing their appearance may cause an episode of angina a sudden attack of breathlessness, or paroxysmal nocturnal dyspnea. In other cases they may be responsible for syncopal attacks or other less severe manifestations of transient cerebral ischemia. The arrhythmias producing these problems may be life threatening in their own right as with ventricular fibrillation or cardiac asystole Other less immediately dangerous arrhythmias will produce or aggravate clinical deterioration by their effect on the cardiac output and in this context it should be emphasized that in a patient with marked atheromatous narrowing of coronary or cerebral arteries even a moderate sinus bradycardia or tachycardia may give rise to symptoms.

In all these cases the clinical picture will be improved only when the arrhythmia and its nature have been identified and appropriate treatment instituted. In many cases however in spite of strong clinical suspicion the diagnosis may be inevitably delayed as one may see the patient at a time when the arrhythmia is not present in any form either clinical or electrocardiographic In an attempt to arrive at a rapid diagnosis the patient is usually admitted to hospital and monitoring of his cardiac rhythm is performed for an indefinite period Cardiac monitoring may also be carried out on an outpatient basis with a system such as the one devised by Holter[1] and the advantages and results obtained by this means have been reported[2] A variable degree of success may be obtained with these methods which have a definite place in our diagnostic armamentarium but on occasions prolonged monitoring proves fruitless as there is a limit to the length of time that monitoring can be carried out

I have used some simple procedures in these patients which have often led to an early diagnosis and I feel that

Intractable CHF

Catecholamines are not often used in the treatment of severe CHF Norepinephrine and epinephrine although they will increase cardiac output have a detrimental effect on myocardial function because of the increased peripheral resistance or afterload that they produce In addition, they increase renal vascular resistance with a resultant decrease in sodium excretion

Isoproterenol will be beneficial to the failing heart by decreasing peripheral resistance or afterload in patients with primary myocardial disease or with nonobstructive valvular lesions Isoproterenol will decrease mitral and aortic regurgitation by lowering peripheral resistance Isoproterenol is detrimental in patients whose failure is secondary to mitral stenosis The increase in heart rate and cardiac output will result in an increase in left atrial left ventricular gradient In aortic stenosis the increase in stroke volume will increase the left ventricular aortic gradient and therefore will increase left ventricular work

Dopamine increases cardiac output, has little effect on heart rate decreases peripheral resistance and in addition decreases renal resistance with a resultant increase in sodium excretion Dopamine functions as an inotropic diuretic Continuous dopamine infusions (5 to 10 μg per kilogram of body weight per minute were administered to nine patients in severe intractable heart failure All patients were digitalized on low sodium diets and no longer responded to large oral doses of diuretics or even to the intravenous administration of 200 mg of furosemide or 100 to 200 mg of ethacrynic acid alone or in combination with acetazolamide or hydroxychlorothiazide After the dopamine infusion produced an initial increase in urine flow, intravenous furosemide 80 to 120 mg produced a significant diuresis Dopamine was continuously administered for up to 14 days with marked clinical improvement Although five of the nine patients died because of irreparable cardiac disorders, these preliminary observations are sufficiently encouraging to warrant further clinical investigation

It has been observed at Montefiore Hospital, as well as reported by others that a combination of dopamine and phentolamine, norepinephrine and phentolamine and dopamine and norepinephrine on occasion has resulted in clinical improvement whereas a single drug alone has not been beneficial

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In all these cases the clinical picture will be improved only when the arrhythmia and its nature have been identified and appropriate treatment instituted. In many cases, however, in spite of strong clinical suspicion, the diagnosis may be inevitably delayed as one may see the patient at a time when the arrhythmia is not present in any form, either clinical or electrocardiographic. In an attempt to arrive at a rapid diagnosis the patient is usually admitted to hospital and monitoring of his cardiac rhythm is performed for an indefinite period. Cardiac monitoring may also be carried out on an outpatient basis with a system such as the one devised by Holter[1] and the advantages and results obtained by this means have been reported.[2] A variable degree of success may be obtained with these methods which have a definite place in our diagnostic armamentarium, but on occasions prolonged monitoring proves fruitless as there is a limit to the length of time that monitoring can be carried out.

I have used some simple procedures in these patients which have often led to an early diagnosis and I feel that

these should be tried in addition to the well established methods cited above During the original interview with the patient the exact circumstances present when the attacks occur should be carefully extracted from the history and with luck one may be able to record an arrythmia in hospital by simulating those circumstances with the patient connected to an ECG machine An attack of cerebral ischemia may be described as occurring only with exercise and a rapid supra ventricular arrhythmia or multiple ventricular ectopics may be noted on a previously normal resting ECG if the patient exercises If this line of enquiry does not provide the answer I then ask the patient to hold his breath at the end of a deep inspiration and then at the end of a deep expiration I finally record the rhythm during and immediately following a Valsalva maneuver I have in this way sometimes precipitated a mild attack while obtaining a diagnostic change on the concurrent FCG tracing Variations in the degree of vagal tone arterial pressure venous return to the heart, and exaggerated responses of the arterial baroreceptors are possibly in some way responsible for this phenomenon In this context it should be remembered that patients who are receiving drugs which block vasomotor nerves may faint while performing the Valsalva maneuver In these cases however there will be no change in the heart rate or rhythm on the ECG recording

Should these simple procedures fail to give a satisfactory diagnosis I then teach the patient and relatives how to take the pulse at the wrist. This simple skill is easily acquired by most people after just a few minutes instruction They are then advised to take the pulse whenever an attack appears to be imminent during the attack and for a time following it If an attack tends to occur during a particular activity they are urged to take the pulse at intervals during the performance of that activity whether or not the patient is aware of any symptoms They may be advised in addition to take the pulse at regular intervals during the day On each of these occasions they are asked to note the pulse rate and any irregularity in the rhythm and a record of these observations should be kept

Whenever an attack occurs the patient is urged to go to the hospital as soon as practicable He should be provided with an explanatory letter which he should always carry to advise the Emergency Doctor he first sees at the hospital of the problem and of the importance of an immediate ECG recording

It should be strongly emphasized that very often a rhythm or conduction disturbance is present in *some* form for some *time after subsidence* of the patient s symptoms This may take the form of a prolongation of the P R interval or occasional dropped beats or multifocal ventricular ectopics, and their observance may prove invaluable A patient I recently encountered developed symptoms of marked cerebral ischemia for a full ten minutes *before* any disturbance in the cardiac rhythm was apparent on the ECG Only then did an extremely slow sinus bradycardia appear which was soon followed by a nodal bradycardia with multiple multifocal ventricular ectopics This arrhythmia persisted unresponsive to intravenous atropine until pacing had been established about fifteen minutes later Although the sequence of events in this case is most unusual and the reasons for it unexplained it does serve to emphasize the fact that it should never be considered too late to record an ECG rhythm strip after such an episode

Once these diagnostic aids have been exhausted with negative results and if suspicion of a transient abnormal rhythm is strong in some cases it may be justifiable to treat on the basis of a probable although unproved diagnosis The main difficulty now is that the nature of the arrhythmia is not clear and any choice of treatment be it drugs or cardiac pacing will be somewhat haphazard This step illogical as it may appear at first sight may well be justified in a situation where intelligent guesswork may save the patient s life or cure his symptoms As always one should carefully watch that an iatrogenic complication is not added to the clinical picture and the possible risks of any therapy will have to be carefully weighed against its expected benefits

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Should we always keep controlling?

Both patient and doctor take it for granted that many patients are kept under control

Very often the doctor does not realize that this being kept under control is a stress for the patient *If there were no risk* of something turning up he would not ask me to come back " thinks the patient The patient never gets rid of his disease

Is it really wise to keep the patient under control? It was surprising to find in *analyzing* the data of a double blind trial *in patients operated* upon for the first stage of lung cancer [1] that it did not make any difference in the well being and survival rate whether they were *regularly seen* by their doctor or paid him a visit only when they had complaints *Regular* control showing itself unneccessary in this particular situation the question arises whether or not, in many other

situations it is superfluous to keep the patient under control

Of course there are situations in which a regular control is a must or at least desirable e g patients being treated with anticoagulants antihypertensive drugs or quinidine patients for whom regularly visiting their doctor is the only way to insure their regime and therapy patients needing continuous reassurance or encouragement.

But will it not be much better for many other patients to determine for themselves when they will see their doctor (assuming that they have been well instructed)?

Generally speaking one may say that regular control of a patient is desirable as soon as there is a chance that the doctor will detect a disease or deterioration of a disease—while the patient feels no symptoms at all—in an early phase when help can be given which would be impossible in a later phase But how often will this happen?

There is a large group of patients who visit their doctor with the regularity of the clock only to hear that they can continue their regime and therapy Most of these visits are superfluous In most cases it is a complaint or signal of the patient which is the basis of changing the therapy Before ordering a patient to come back the doctor should ask himself if his instruction is sensible It may be wiser to ask the patient to return whenever he feels he needs it

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Chlorambucil in the treatment of systemic lupus erythematosus

Cytotoxic drugs have been used to treat patients with systemic lupus erythematosus (SLE) since before the introduction of corticosteroids.[1] In recent years, with recognition of the risks and discomfort to the patient from the high doses of prednisone that may be required in this disease [2] this group of drugs has attracted increasing attention The rationale is now basically the same as when nitrogen mustard was first used that the immunosuppressive potential of these drugs might be exploited in a disease where there is autoantibody formation and immune complex deposition

Controlled clinical trials of treatment in SLE are difficult because of the relative rarity protean nature and unpredictable course of the disease Indeed, this clinical diversity probably reflects differences in immunopathology natural history [3-5] and conceivably response to treatment Nevertheless the well-conducted controlled clinical trial remains the most effective available method for assessing different forms of treatment.

Of these nonsteroidal immunosuppressive drugs moderately encouraging results have been reported with azathioprine[6,7] and with cyclophosphamide [8,9] Cyclophosphamide was superior by several clinical and laboratory criteria to azathioprine which was in turn superior to placebo in a double blind study of their effect in lupus nephritis.[10]

Experimental evidence can be adduced to support the choice of either of these drugs Cyclophosphamide will suppress antibody response after antigenic challenge[11,12] and is effective in the murine model of human lupus.[13] Azathioprine performs poorly by comparison but is effective in suppressing graft rejection. Species differences and the design of therapeutic schedules can radically affect the results of such experiments[14,15] Indeed, the clinical correlations of suppressed immune response are by no means clear [16,17]

All of this group of drugs carry appreciable risks from marrow depression and some from cytotoxic effects on other tissues Patients with SLE may be at particular risk from marrow depression because of a reduced marrow reserve [18] In a recent well conducted clinical trial of cyclophosphamide in rheumatoid arthritis the dose required to exert a clearly beneficial effect upon the disease carried with it a high incidence of toxicity [19] Chemical cystitis may be prevented by intermittent intravenous administration with hydration, but alopecia may occur in up to half of the patients treated with cyclophosphamide [20,21] The magnitude of the risk of the long term induction of tumors has yet to be assessed, although on present data it appears to be somewhat greater with azathioprine [22] The over all incidences of complications from these two drugs were recently found to be comparable [23] There is however apparently no risk from gonadal damage with azathioprine whereas this is a likely accompaniment of cyclophosphamide treatment.[24]

Chlorambucil like cyclophosphamide a derivative of nitrogen mustard has been used extensively in Europe to treat connective tissue disorders although there is a paucity of objective reports.[25] In the United States and Britain it is principally used to treat lymphoproliferative disorders and cold agglutinin hemolytic anemias [26] Its use is reported in treating patients with SLE.[27] This drug was chosen largely because of favorable experience with it as regards side effects in treating patients with connective tissue diseases and hematologic disorders This accords with other opinions that it is reliably absorbed, relatively progressive and predictable in its action on the marrow with a low risk of significant marrow depression.[28-30]

In the report cited, four of the six patients had a histologic diagnosis of focal glomerulonephritis and one proliferative glomerulonephritis In all of these patients renal function

was deteriorating prior to the introduction of chlorambucil In one patient azathioprine had previously been associated with a temporary improvement in renal function which had subsequently deteriorated despite continuous treatment with azathioprine All were experiencing unacceptable steroid toxicity Following the introduction of chlorambucil renal function improved in all and prednisone could be reduced or withdrawn Repeat biopsies in two patients showed histologic improvement by a point counting technique These patients were on chlorambucil for 24 to 64 months and all remain well respectively 6 5 5 3 and 1½ years after commencing treatment with chlorambucil The sixth patient was given chlorambucil because treatment with prednisone for six years had failed to control episodes of hemolysis skin ulceration and other manifestations of vasculitis. Subsequent to the introduction of chlorambucil her condition progressively improved and the dose of prednisone could be reduced with alleviation of corticosteroid side effects She remained well up to the time of writing two years later

In all the patients LE cells disappeared from the peripheral blood as the clinical condition improved and in five the antinuclear antibody titer became negative Other immunologic parameters such as DNA antibody measurements were not available at the time the patients were treated.

One patient developed a degree of lymphopenia and one of neutropenia which recovered promptly with reduction in *dosage One* patient developed a moderate pancytopenia which did not fully recover These were presumed to be effects of chlorambucil In one patient menstruation had ceased at the age of 34 six years before the introduction of chlorambucil to her treatment presumably as a result of her disease and high dosage steroid therapy One patient aged 34 developed amenorrhea one year after starting chlorambucil and others aged 34 35 and 38 each after three years of chlorambucil treatment Cyclophosphamide was associated with azoospermia within six months of commencing treatment in all of 31 patients described by Fairley and associates [24] Amenorrhea occurred in 18 of 34 menstruating women on average within seven months of commencing cyclophosphamide [31] Chlorambucil may therefore hold little advantage over cyclophosphamide in this respect unless it can be shown that there is a real difference between the drugs as regards the duration of treatment before the effects on the gonads become manifest

The paper cited does not report a controlled trial and it is possible that all six patients experienced a spontaneous remission of their disease Further critical evaluation of chlorambucil will be required to assess its usefulness in the management of patients with SLE Cytotoxic drugs are being used with increasing frequency for this purpose but against their as yet uncertain benefits must be set the well established risks to the patient from the drugs most often suggested Although chlorambucil is by no means an innocuous drug its ease of administration and relatively predictable action indicate that its potential as an immunosuppressive agent in the treatment of SLE warrants further examination

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Letters to the Editor

Aneurysmectomy for recurrent ventricular tachyarrhythmias

To the Editor

The article entitled Aneurysmectomy for recurrent ventricular tachyarrhythmias by Welch Fontana and Vasko (AM HEART J 85 685 1973) leaves the reader with the impression that ventricular tachyarrhythmia due to ventricular aneurysm is a very rare phenomenon According to the authors only six cases were reported where ventricular tachycardia was the sole manifestation of ventricular aneurysm and only five cases where ventricular aneurysmectomy was performed in order to overcome recurrent ventricular tachyarrhythmias

We believe that life threatening tachyarrhythmias due to ventricular aneurysm are much more common than is reflected by the article In the last years we have been searching for ventricular aneurysms by angiocardiography (using the right sided approach with injections of contrast material in the main pulmonary artery[1]) in all our cases of arteriosclerotic heart disease suffering from repeated ventricular tachyarrhythmias By doing so we succeeded in eliminating life threatening ventricular tachyarrhythmias in seven patients by ventricular aneurysmectomy

Our first patient who underwent ventricular aneurysmectomy for severe rhythm disturbances[2] has now been followed at our outpatient clinic for 3½ years (after the operation) and an undisturbed sinus rhythm is present without the need of any antiarrhythmic drug

It is our opinion that ventricular tachycardia as the only manifestation of ventricular aneurysm is much more common than mentioned by the authors and that more patients with life threatening tachyarrhythmias might be saved by ventricular aneurysmectomy

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Reply

To the Editor

We fully agree with Drs Neufeld Schlesinger and Lieberman that ventricular tachyarrhythmia due to ventricular aneurysm is indeed not a very rare phenomenon It was also the experience at our institution that this was not unusual and we were surprised upon review of the literature to find a paucity of cases that had been previously reported However since aneurysmectomy for recurrent ventricular tachycardia represents such a dramatic surgical cure and because of the relative paucity of the previously recorded literature we felt that this phenomenon should be brought to the attention of those who perhaps do not work in large institutions and would not see this clinical situation as frequently

Careful left ventriculography for the demonstration of aneurysmal areas of the left ventricle in patients with arteriosclerotic heart disease who have recurrent ventricular arrhythmias in order to define the presence of an aneurysm is essential in the total clinical management of patients with this particular symptom complex

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Thromboembolism and oral contraceptives

To the Editor

Dr Cecil Hougie has reviewed the literature on thromboembolism as a possible side effect of oral contraception and has concluded that " the available evidence favors the opinion that oral contraceptives do not predispose toward thromboembolic disease This conclusion may or may not be correct. A decision as to that cannot now be made Still Dr Hougie s conclusion requires comment because of the arguments used in reaching it (Hougie C Thromboembolism and oral contraceptives AM HEART J 85 538 1973)

To Dr Hougie s credit he indicates early in his paper that the issue is not over the observations that have been made but rather over their proper interpretation The specific issue is whether available evidence will sustain the inference of a causal relation of oral contraception to thromboembolism Dr Hougie appears to accept the criticisms that have been made of the material summarized by Drill and Calhoun, and this publication plays no important role in the argument The prospective study of Fuertes de la Haba and his group is the essential epidemiologic keystone in his rejection of a causal interpretation of the association that has been observed in three major retrospective studies Five reasons are given for this (1) retrospective studies reveal associations, not cause and effect relations (2) inferences made from the results of such studies may later be proved incorrect (3) if fallacious results are produced by one retrospective study then all other such studies on the same question will produce fallacious results (4) the interpretation is not supported by ancillary studies of clotting factors or by histologic findings in vascular abnormalities that occurred in women using oral contraceptives and (5) an alternative hypothesis involving the difficulty of diagnosing thromboembolism is consistent with all relevant data

That the association was not observed in a prospective study has not been listed as a reason for rejecting the retrospective data To do so would be a disservice to Dr Hougie It would in effect charge him with circular reasoning that is with using the truth of the prospective data to demonstrate the falsity of the retrospective data and to conclude therefrom that the prospective data are true I believe Dr Hougie recognizes that the logical problem is to find grounds external to the two sets of observations for choosing between them

Returning to the five points listed above it may be noted that they are of two types Reasons 1 2 and 3 concern the value of the retrospective method for producing valid information Reasons 4 and 5 concern the logic of assessing empirical information to accept or to reject an inference of causation

With regard to the validity of observed associations to expect that the retrospective method should do more than pro

vide an empirical basis for fallible causal inferences is expecting more of it than of any other method for making observations There is no empirical process by which a cause and effect relation can be demonstrated. Causation is always inferred, and whether made from data gathered retrospectively or otherwise such may prove to be false

Moreover the retrospective method of study is very general and this name conveys none of the fine points of methodology that distinguish good from bad research. The validity of observations made retrospectively is determined by the care given to such elements of method as case finding selection of controls measurement and analysis not by the general character of the study design. A poorly designed or poorly executed retrospective study may produce incorrect observations A well designed and executed retrospective study is less likely to do so Results from a poor study and those from a good study may not agree To the ex ent that they are approximations to the same underlying truth however results from well designed retrospective studies are likely to agree This is the principle of replication. All of these statements are equally applicable to prospective epidemiologic studies and to experimentation.

There are no established logical rules for inferring causation from empirical association When doing so it is useful if the association observed by one method of study is consistent with observations made by other methods Such consistency however is neither necessary nor conclusive Lack of supporting observations cannot be interpreted to mean that such will never be made Knowledge at any given time is limited by resources, by available technology and by the imagination of people who make observations An apparent conflict between results obtained by two methods could mean that our interpretation of one or the other set of data is incorrect Even so it does not tell us which is correct and which is not. Such a conflict may mean only that our understanding is deficient Clarification of apparent conflicts usually comes only after further observation, and the necessary observation may be made tomorrow next week, or next year

It is also useful to formulate explicitly and to evaluate empirically all possible alternative hypotheses that may explain an observed association without invoking causality These measures however are rarely adequate to rule out a causal hypothesis with full certainty Clearly conceptualization of an hypotheses without independent evidence of its truth is insufficient This merely leaves us with two plausible but unsupported interpretations Even independent evidence of the truth of an alternative hypothesis rarely can be interpreted to mean that causation is not involved in the association to be explained. It has not often been possible to form alternative hypotheses to be mutually exclusive and it is often found that both are applicable

The particular alternative advanced by Dr Hougie has to do with the possibility that diagnosis of thromboembolism was influenced by knowledge of the use of oral contraception Dr Hougie acknowledges that attempts were made in the retrospective studies to examine this hypothesis and that its truth is debatable He apparently does not recognize that this alternative could be tested directly in either a retrospective or prospective epidemiologic study Most important, he offers no more than speculation to support this alternative and responsible science does not end with speculation.

Dr Hougie s arguments for rejecting a causal interpretation of the association of thromboembolism to oral contraception are weak Numbers 1 2 and 3 are invalid number 4 is inconclusive number 5 is incomplete Beyond this it is constructive both scientifically and medically to act as if the causal interpretation were true This interpretation has led to development of low dosage contraceptives it provokes further inquiry into mechanisms of fertility contraception, and thrombosis and it indicates caution in the prescription of oral contraceptives Denial of the possibility of a causal relation is not nearly so stimulating as this

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Reply

To the Editor

Dr Nefzger believes that my statement that the diagnosis of thromboembolism in the major retrospective studies on the pill was influenced by knowledge of the use of oral contraceptives is debatable But surely there is no dispute as to the fact that some of the physicians engaged in these studies were aware that their patients were on the pill and had also read reports that the pill predisposed to thrombosis. In the light of these facts, I think one is on fairly firm ground in believing that, in at least some cases this knowledge influenced the diagnosis. To eliminate this factor in any future retrospective study when more physicians than ever are under the impression that an association between the pill and thrombosis has already been established seems to me to be virtually impossible This is what I meant when I stated that further retrospective studies are unlikely to shed further light on the problem.

There are other reasons for not accepting the generally accepted causal interpretation of the retrospective studies. These have been very clearly outlined by the eminent epidemiologist and physician, Dr Feinstein,[1] who concludes that at least two of the five criteria for scientific validity for retrospective studies were grossly violated in the three major retrospective studies on the pill Accordingly I remain convinced that no association has been demonstrated as of now in any type of study

I also question Dr Nefzger s statement that the causal interpretation led to the development of low dosage contraceptives. Well before the allegations of a causal relationship between the pill and thromboembolism were made the pill was well known to produce undesirable side effects but aside from this, good therapeutics dictates that the dose of any drug should be as low as possible compatible with maximum efficiency of action. The hypothesis of a causal relationship may have served a useful purpose but this is not a reason for permanently retaining it in the absence of supportive scientific evidence However I am pleased that Dr Nefzger agrees that an association between oral contraceptives and thromboembolic disease has not been established and this was the main point of my review

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Measurement of bradykinin

To the Editor

I have read with great interest the article by Kimura and associates entitled "Changes in bradykinin level in coronary

Letters to the Editor

Aneurysmectomy for recurrent ventricular tachyarrhythmias

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The article entitled Aneurysmectomy for recurrent ventricular tachyarrhythmias by Welch Fontana and Vasko (AM HEART J 85 685 1973) leaves the reader with the impression that ventricular tachyarrhythmia due to ventricular aneurysm is a very rare phenomenon According to the authors only six cases were reported where ventricular tachycardia was the sole manifestation of ventricular aneurysm and only five cases where ventricular aneurysmectomy was performed in order to overcome recurrent ventricular tachyarrhythmias

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With regard to the validity of observed associations to expect that the retrospective method should do more than pro

Two days later I developed pain in my left testis with fever and pain at the tip of the penis and suprapubic region during micturition Seven days in bed settled this left sided orchitis, but I was left with some testicular atrophy which subsequently completely recovered. My temperature again gradually settled but continued to show an afternoon and evening rise to about 100 F

While life was bearable in the mornings, allowing some paper work to be done an indescribable *feeling of general* malaise would descend after lunch This feeling demanded capitulation to bed without *further ado on* most days By this stage a Coxsackie virus had been isolated from my stools and a rising titer of antibody *against* Coxsackie virus strain B2 was eventually demonstrated serologically I was advised to rest and be patient but progress was slow

I eventually returned to work 2½ months after my first *symptoms*. The idea was to do part time work initially but this proved difficult as only morning work was feasible Considerable friction developed between colleagues and myself and, although I cannot speak for them I think the consensus was that I was either swinging the lead or suffering from postviral depression. Both these suspicions I deeply resented, but how could I rebut them? An evening temperature of 100 F looks trivial but it was my only objective evidence of ill health. Indescribable general malaise muscle pain, and lethargy cannot really be quantified. After pressure from senior colleagues blood was taken for a full blood count E S R and muscle enzyme levels All of these investigations were normal and the E S R never went above 2 mm in the first hour which I felt strengthened some of my colleagues theories In retrospect I was very thankful that I had had sufficient wit to ask my wife to take blood for viral serology for without concrete evidence of an enterovirus infection I have no doubt I would have ended up in the care of the psychiatrists

Two weeks after returning to work I began to get runs of tachycardia with a rate of up to 160 per minute After calling my general practitioner at some ungodly hours a cardiologist was summoned with all his electronic equipment The tachycardia proved to be a sinus tachycardia. I was reassured that *tachycardia* is a familiar feature of Coxsackie infections and that perhaps I was too worried about myself There is no doubt I was concerned but I felt my affect was congruous I have *never felt so ill in my life*

A fortnight later I returned to work again. This left me exhausted for the next two months beyond anything I can ever remember During this period I continued *to have an evening* fever of up to 100 F and muscle pain. Five months after the start of my illness one of my daughters put the thermometer down the sink—perhaps the best place for it—and my temperature record ceased.

By this stage the state of the game was such that I told everyone that I was completely recovered. It was much more simple than trying to explain. The story has a fairly happy ending I now feel fit, 18 months later but still experience muscle pain if I am rash enough to drink spirits red wine or more than three pints of beer and a round of golf is not as easy as it used to be

What did I learn from this illness? Several things First I learned what general malaise really means Second, Bornholm disease in the young adult need not be short lived. Most important, I learned how difficult it is to communicate with doctors. We expect a lot from our patients.

Since publishing an earlier account of this illness[1] I have received several letters from doctors who have experienced Bornholm disease Most of these writers stress the frank disbelief of their medical attendants that this disease can be anything but short lived. I should be interested to hear from *anyone who has had Bornholm* disease A severe Coxsackie infection is an event not easily forgotten.

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sinus blood after the experimental occlusion of a coronary artery which appeared in the June 1973 issue of the JOURNAL.

It is a well known fact that the measurement of bradykinin by bioassay using the contraction of guinea pig ileum is highly inaccurate not quantitative and subject to a great deal of experimental error It would have been a great deal simpler to place a cannula in the femoral artery connect it to a Statham transducer and measure bradykinin release in each animal according to the degree of hypotension obtained [1]

The changes in pH Po_2 and Pco_2 in coronary sinus blood relevant to bradykinin release are meaningless as depicted in Figs 5 to 7 without proper statistical analysis Finally the relationship of bradykinin to anginal pain in ischemic heart disease remains unanswered

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Reply

To the Editor

We agree that the bioassay of bradykinin is not accurate and measurement errors cannot be avoided as we stated in the discussion in our paper However the elevation of bradykinin level in coronary sinus blood after ligation of anterior descending branch was confirmed with a statistical significance in our experiment. This means that, even if the method is not sufficiently accurate elevation of bradykinin level is regarded as valid

The hypotension method pointed out by you has not been employed by us We would like to test this method on the next occasion

As you pointed out the changes in pH Po_2 and Pco_2 in coronary sinus blood are not related to bradykinin release as far as concerned with Figs 5 to 7 However the parameters in these figures were measured simultaneously Because pH Po_2 and Pco_2 may change in succession it is necessary to analyze the changes of these levels sequentially The results of such analysis in individual cases are illustrated in Figs 8 to 10 in which relationships between these parameters can be seen

Thank you very much for your excellent comment.

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The Devil s grip

To the Editor

I should like to report my personal experiences during an illness caused by a Coxsackie B2 virus

This illness began in my family innocently enough It was late summer the sun was shining and I was on holiday After visiting a museum my eldest daughter then aged six years complained of pain in the right side of her chest and right upper abdomen and asked to be carried I thought this was a bit of attention seeking behavior and support for this hypothesis appeared to be forthcoming when ten minutes later she was running around with no apparent disability However her pain returned at the same site within a few minutes and was obviously made worse by respiratory movements. She was also febrile (temperature 101 to 103 F) but there were no abnormal signs in either the chest or the abdomen at this or any subsequent stage The pain was strikingly intermittent with some pain in the left shoulder but again apparent recovery occurred after three days All the symptoms reappeared 24 hours later but complete recovery occurred after a week.

Her two younger sisters then aged four and two years, developed an identical illness within four days. The intermittent character of the chest and abdominal pain with rather unexpected preservation of a normal appetite were notable features

Three days after the start of my eldest daughter s illness, I felt generally unwell and irritable with low-grade fever and muscle aches and pains especially in the back and neck. Over the next 36 hours my temperature rose to 102 6 F and the muscle pain became much more severe especially during the night This symptom was so striking and intense and so unlike anything I had experienced before that I decided to keep a record of events The pain began in both legs, later spreading to the upper abdomen chest and both shoulders. A deep breath intensified the pain in both trunk and shoulders The pain was of two distinct types there was a general almost unrelenting background ache in the limbs and the shoulders and a more severe stitch like pain particularly in the trunk This latter pain came usually in lancinating episodes lasting at most five minutes rather than seconds and seemed to affect areas of muscle about 5 cm in diameter This pain after a brief interval of freedom would return to the same area of muscle or to an area which seemed closely adjacent Surprisingly at this stage the muscles were not tender on palpation

The fever and muscle pain were accompanied by severe sweating a mild sore throat, painful eyeballs and bilateral testicular pain with dysuria and some difficulty in micturition with terminal dribbling I also experienced transient undue sensitivity to noise which lasted for about three hours.

The muscle pain fever and other symptoms gradually settled and by the sixth day I had again taken my family on a long promised visit by car to a zoo some 60 miles away I was most irritable during this day and returned home with a headache which gradually became more severe and bursting accompanied by neck stiffness and fever of 101 8 F A marked band of hyperesthesia developed around my chest, especially noticeable laterally and persisted for several hours I also noted a marked feeling of depersonalization and derealization at the height of the fever The general practitioner who attended me at this stage observed that I had a tachycardia out of all proportion to the height of my temperature After about three days the headache neck stiffness, and fever gradually settled but I was left with some generalized muscle tenderness and a low grade fever present only in the afternoons and early evenings

On the fourteenth day of the illness I went to convalesce at the coast and my temperature became normal again 2 days later Encouraged I went to watch a county cricket match This proved to be so exciting that my father who was with me had what appeared to be a cardiac arrest (from which he eventually recovered) the following day my grandmother died These two events put an end to my convalescence

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Editorial

What is transposition of the great arteries?

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The term transposition of the great arteries has been used in four different senses in the literature Earlier writers used it when the great arteries were altered in their relationship to their respective ventricles. The first case of transposition was described by Baillie[1] In his case the aorta arose out of the right ventricle and the pulmonary artery out of the left. von *Rokitanski*[2] considered that all forms of transposition were the result of abnormal rotation of the aortic septum which being unable to meet the ventricular septum resulted in one or *both vessels* apparently arising from the wrong ventricle

Reversal of the anteroposterior relationship of the aorta and the pulmonary artery in transposition was commented upon by various workers as early as the nineteenth century Kurschner[3] observed that in transposition there was a reduction in or lack of the normal spiral twist of the pulmonary artery about the aorta The *anterior* position of the aorta in transposition was also noted by Keith[4] who pointed *out that in* transposition the aortic portion of the bulbus expands and the pulmonary portion atrophies and such a process results in an anteriorly situated aorta and in the right ventricle de la Cruz and da Rocha[5] and Cardell[6] defined transposition as reversal of the anteroposterior position of the aorta and the pulmonary artery van Mierop and Wiglesworth[7] defined true *transposition of the* great arteries as that condition *in which the* aorta lies anterior to the pulmonary artery and originates from a morphologic right ventricle anterior to the crista supraventricularis or its remnant. The pulmonary artery may originate from either ventricle or *override a defect* Shaher[8] considered transposition to mean reversal of the *anteroposterior* relationship of the aorta and the pulmonary artery since the transposed arteries may arise from one ventricle as in double outlet right ventricle or single ventricle or each vessel from a separate ventricle as in complete transposition or corrected transposition

Other writers used the term transposition to *signify any* alteration in the position of the great arteries Thus Abbott[9] defined transposition as an *alteration* in the position of the two great vessels relative to the ventricles of the heart, or to each other at their origin so that they spring *either from* reversed ventricles—the aorta from the right and the pulmonary artery from the left chambers (complete transposition)—or from the *ventricles* to which they normally belong but in reverse relationship *(corrected transposition)* Harris and Farber[10] pointed out that this definition *is too* vague and suggested that an alteration in the anteroposterior *relationship of* the great vessels either at the ventricular insertion or in their spiralling should be added to Abbott s

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Cardiac pacing Edited by Philip Samet M D New York and London 1973 Grune and Stratton Inc 427 pp $21 00

This publication on cardiac pacing is one of the series of clinical cardiology monographs Dr Samet is certainly highly qualified to edit such a book He gathered a large number of contributors who have been studying and using cardiac pacing in the practice of cardiology As in monographs of this type the editor organized the book to review the important aspects of the problem of cardiac pacing Among the subjects discussed are history anatomy and pathology of the conducting system engineering aspects physiology electrocardiography indications for pacing technique and pacemakers There is a good bibliography included with each paper The monograph is comprehensive Samet has rendered an excellent service to all physicians who can now find the important aspects of cardiac pacing in a single book The presentations are directed to the clinician Obviously the physician using cardiac pacing must be a mature cardiologist as this procedure is used in patients with serious disease This is a very good contribution to the medical literature

***The Paul D White symposium on cardiovascular disease* Major advances in cardiovascular therapy** Edited by Henry I Russek M D Baltimore 1973 The Williams & Wilkins Company 462 pp $35 00

This publication of the papers presented at the Paul D White symposium on cardiovascular disease is another report of the American College of Cardiology-St Barnabas Hospital Symposia on Cardiology The subjects discussed were concerned with the major advances in cardiovascular therapy The book contains many papers of wide interests. For example they range from discussions of subcellular concepts to clinical diagnosis and treatment Myocardial infarction hypertension disorders in cardiac rhythm and surgical treatment are among the main subjects discussed by several speakers The publication is a good one The clinical aspects of various problems are emphasized and kept in focus This is another useful and valuable publication from the annual symposia so ably organized and conducted by Henry Russek in December of recent years

The sounds of the diseased heart By Aldo A Luisada M D St Louis 1973 Warren H Green Inc 391 pp

This book on sounds of the diseased heart is the second monograph by Dr Luisada who has devoted most of his research studies to heart sounds in normal and diseased hearts. Luisada has performed an excellent service to clinical medicine and cardiology in producing this book There is no doubt that expert auscultation of the heart is essential for excellent service to patients regardless of the physician s field of inter st The illustrations and text in this book are well selected and clear The correlations of heart sounds with hemodynamic phenomena and recordings as well as the clinical status of the heart is nicely done and renders this book useful not only to all doctors but medical students as well Luisada s book is highly recommended to all doctors and students Internists general practitioners and cardiologists will certainly appreciate this book.

Peripheral vascular surgery By Bok Y Lee M D F.A.C.S., and Frieda S Trainor M A Ph.D New York, 1973 Appleton Century Crofts, 270 pp $16 50

Drs Lee and Trainor have emphasized the importance of the configuration of the arterial pulsatile curves of the lower extremities in the diagnosis and surgical management of the peripheral vascular disease They used impedance plethysmography to a large extent indicating however that Doppler ultrasound and direct electromagnetic flowmetry are also available Direct electromagnetic methods require direct exposure of the vessel to be studied. The authors fail to emphasize sufficiently that these methods are directly concerned with a given vessel except for the method of impedance plethysmography and that method is difficult to standardize All these (three) methods are suitable for recording changes following a surgical procedure for occlusive vascular diseases The authors present clearly their ideas concerning the slopes of the pulsatile curves obtained by their recorders, but they fail to emphasize sufficiently the marked normal variations that can occur in the magnitude and configuration of such curves. These variations require careful interpretation and understanding of peripheral vascular physiology and environmental control The proper clinical use of the techniques outlined in this book requires a thorough knowledge of the behavior of the circulation in health and diseases Changes are described for large diseased arteries following sympathectomy arterial grafts, and combined procedures There is an interesting chapter on the fallibility of the peripheral pulse The peripheral arterial pulsation may be misleading to the less informed clinicians but it is rarely true that the pressure volume and nature of the peripheral arterial pulse noted merely by palpation at the bedside is not extremely valuable The mere presence of a good pulsation in the distal arteries is a sign of good arterial flow This reviewer finds that this book is interesting but it tends to overemphasize for clinical purposes the configuration of a recorded arterial pulse However physicians interested in the peripheral circulation will want to read this book to learn the ideas of the authors concerning their approach to peripheral vascular surgery

Hypertension XXI Hypertension in man and the experimental animal Edited by James C Hunt M D New York 1973 The American Heart Association 186 pp $5 00

This volume on hypertension represents a collection of the 16 papers presented at the meetings of the Council for High Blood Pressure Research of the American Heart Association. The subjects discussed ranged widely and included animal and human experimentation Discussion of aldosterone regulation adrenergic receptor function sodium balance the renin angiotensin system radioimmunoassay problems and genetic control of blood pressure were among the subjects discussed Those who subscribe to *Circulation Research* already have this publication

workers in this field agree on what defines transposition the majority would probably agree that the presence of either or both of these two anatomical situations would constitute transposition (1) reversal of the anteroposterior relationship of the aorta and the pulmonary artery regardless of the proximal connection of these arteries (2) origin of the aorta completely from the morphological right ventricle and the pulmonary artery completely from the morphological left ventricle regardless of the anteroposterior relationship of these vessels

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definition A modification of Abbott s definition was used by Lev and Saphir,[11] Lev,[12] and Edwards [13] According to Lev, transposition of the great vessels is 'an alteration in the position of the two great vessels relative to the ventricles of the heart or to each other at their origin " Similarly Edwards defined transposition as any congenital abnormality in the relationship of the great vessels (or their remnants) to each other and to the ventricles As pointed out by van Mierop and Wigglesworth[7] this definition includes (1) tetralogy of Fallot, (2) double outlet right ventricle and (3) complete or corrected transposition

In 1955 Ivemark[14] pointed out that the conotruncus and the atrioventricular region have one tissue component in common which is a gelatinuous reticulum Grant[15] assumed that in transposition of the great arteries there is a shift in the orientation of the fibroblastic continuum which lines the primitive cardiac tube Normally it holds the aortic part of the truncus in fibrous continuity with the mitral part of the atrioventricular canal He suggested that in transposition truncal septation proceeds normally but the pulmonary part of the truncus is held in continuity with the mitral valve ring van Praagh and associates[16] adopted this view and defined transposition as mitral aortic valve discontinuity or a relatively well developed muscular subaortic conus In 1967 van Praagh[17] rejected that transposition is a reversal of the anteroposterior relationship of the aorta and the pulmonary artery because in transposition the semilunar valves may lie side by side and the transposed aortic valve may actually lie posteriorly to the transposed pulmonary valve He also pointed out that transposition can be present or absent but never partial

In 1971, van Praagh and associates[18] reported four heart specimens in all of which the aortic valve was above the right ventricular cavity and the muscular interventricular septum and the pulmonary valve above the left ventricular cavity The aorta was posterior to the pulmonary artery and aortic mitral valve continuity existed in all A subpulmonary conus was present in all Based on these four heart specimens the authors defined transposition as the condition in which both arteries are placed across the ventricular septum compared with normal aorta arising above the morphological right ventricle and pulmonary artery above the morphological left ventricle For positional abnormalities of the great arteries in double outlet right or left ventricle single ventricle or anatomically corrected transposition[19] or corrected transposition with isolated bulbar inversion [20] the authors designated malposition of the great arteries a term originally used by Janeway [21]

Of the four concepts of transposition Abbott s definition is too vague and includes conditions like tetralogy of Fallot, pulmonary atresia truncus arteriosus etc The concept of aortic valve–mitral valve discontinuity was too rigid and was given up by van Praagh and associates [18] All authors agree that transposition would be present if both great arteries are placed across the ventricular septum compared with normal However this definition rules out conditions like anatomically corrected transposition[19] and congenitally corrected transposition with isolated bulbar inversion [20] These two conditions have the same conotruncal abnormality as complete and corrected transposition respectively, but in each the aorta arises above the morphological left ventricle and the pulmonary artery above the morphological right ventricle It also excludes conditions like transposition with double outlet right or left ventricle or single ventricle For this reason, the term malposition of the great arteries' was suggested by van Praagh to describe these anomalies Moreover what constitutes transposition and what constitutes malposition if one of the transposed great arteries overrides the septum[22] has not been adequately explained

Defining transposition as reversal of the anteroposterior relationship of the aorta and pulmonary artery will not rule out anatomically corrected transposition congenitally corrected transposition with isolated bulbar inversion or transposition with double outlet right or left ventricle or single ventricle However in conditions where the ventricles may lie side by side as in dextrocardia or congenitally corrected transposition the transposed great arteries may actually lie side by side van Praagh s recent concept of transposition with posterior aorta awaits confirmation by other workers

For a long time authorities have differed on what constitutes transposition An early and exciting debate on this subject will be found in the work of Pernkopf[23] and Spitzer[24] and a more recent one in the papers by van Mierop[25] and van Praagh [26] While it seems difficult to have all

Table I Cases of left ventriculography

No	Name	Age	Sex	Type of ECD	Form of pouch	Appearance phase	Pouch/Aorta (%)	Margin of pouch	Mitral insufficiency	Surgery	Course
1	O S	13	F	II	Lobular	Lateral view in systole	20	Irregular	Moderate	+	Death
2	N Y	10	M	II	Saccular	Lateral view in systole	35	Smooth	Moderate	+	Death
3	S T	12	F	II	Saccular	Lateral view in systole	25	Smooth	–	+	Alive
4	Y I	16	M	II	Saccular	Lateral view in systole	30	Smooth	–	+	Alive
5	Y T	5	M	II	Saccular	Lateral view in systole	35	Smooth	–	+	Alive
6	O N	25	F	II	Saccular	Lateral view in systole	40	Irregular	Mild	+	Alive
7	K A	11	M	II	Saccular	Lateral view in systole	25	Smooth	–	+	Alive
8	S M	20	F	II	Saccular	Lateral view in systole	40	Irregular	–	+	Alive
9	K A	11/12	M	II	Saccular	Lateral view in diastole	30	Irregular	–	–	Alive
10	I H	10	F	II	Saccular	Lateral view in systole	30	Smooth	–	–	Alive

Diameter of the pouch/diameter of the ascending aorta

Table II Autopsy findings

No	Name	Age	Sex	Type of ECD	Arising position	Form of pouch	Size of pouch (cm.)	Thickness of pouch (mean mm.)	Attachment of chordae
1	O S	13	F	II	Anterior portion of tricuspid septal cusp	Lobular	1 0 × 0 5	0 5	–
2	N Y	10	M	II	Anterior portion of tricuspid septal cusp	Saccular	1 0 × 0 7	0 7	–
3	K K	33	F	II	Anterior portion of tricuspid septal cusp	Saccular	1 5 × 1 2	1 2	–
4	U A	5	F	II	Anterior portion of tricuspid septal cusp	Saccular	0 6 × 0 5	0 5	–
5	O H	7	F	II	Anterior portion of tricuspid septal cusp	Saccular	0 5 × 0 4	0 8	–
6	W N	10	F	II	Anterior portion of tricuspid septal cusp	Saccular	1 0 × 0 7	0 7	–
7	K S	31	F	II	Anterior portion of tricuspid septal cusp	Saccular	1 0 × 0 6	1 1	–

no specific findings indicative of the presence of tricuspid pouch

Results

Left ventriculographic *findings* In nine cases positive visual identification of the tricuspid pouch was made in the lateral projection in systole and in the remaining one in diastole (Fig 1)

In the anteroposterior projection in systole scalloping of the anterior mitral leaflet can usually be seen The orifice of the tricuspid pouch is located underneath the anterior portion of the anterior mitral leaflet in the autopsy specimen which corresponds to the superior portion of the scalloping mitral shadow on the left ventriculogram in the frontal projection Although contrast medium is generally injected in the vicinity of this portion in the left ventricular lumen in only a few cases is the tricuspid pouch observable (Fig 2)

In the lateral projection in diastole the tricuspid pouch is generally obscured in the opacity of the contrast medium filling the left ventricle The exception was case 9 (Fig 3)

In the frontal projection in diastole the goose neck sign is demonstrated in all cases but the pouch is visible only in case 9 (Fig 4) Six cases were characterized by a saccular bulge with a flat margin three by a saccular bulge with an irregular margin and one by a lobulated bulge

The diameter of the tricuspid pouch measured from its base on the ventricular septum to the summit of its bulge in a state of full expansion was 20 to 40 per cent of the diameter of the ascending aorta Mitral insufficiency was present

Clinical communications

The tricuspid pouch in endocardial cushion defect

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Left ventriculography is considered one of the most reliable measures for diagnosing endocardial cushion defect (ECD) because it demonstrates the characteristic anatomic features involved. Aside from the usual roentgenologic signs such as the goose neck sign and scalloping of the cleft anterior leaflet of the mitral valve a saccular bulge at the base of the ventricular septum protruding into the right ventricle was found in selected cases of ECD as described by Baron and associates [1]

This roentgenologic finding of saccular protrusion was substantiated at autopsy, where seemingly underdeveloped interventricular membranous septum was seen protruding into the anterior third of the septal leaflet of the tricuspid valve forming a pouchlike structure We have termed this bulge tricuspid pouch '

This communication discusses the implications of the tricuspid pouch in ECD as found in our studies of left ventriculograms and autopsy specimens

Materials and methods

This study was based on 82 patients with a clinical diagnosis of ECD seen in the past six years and on 38 autopsy specimens Out of 82 cases of ECD diagnosed by left ventriculography, the tricuspid pouch was found in 10 (Table I)

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Five of the 10 were male and five female their ages ranged from 11 months to 25 years.

In eight of the 10 patients the presence of the tricuspid pouch was confirmed during an open heart operation and the intracardiac anatomy was compatible with Grade II ECD, according to the anatomic classification of Campbell and Missen [3] Two of the 10 died postoperatively, one of complete A V block and the other of low cardiac output syndrome and autopsies were performed (cases 1 and 2)

In the two patients who were not operated upon, a clinical diagnosis of Grade II ECD was made on the basis of their clinical symptoms, cardiac catheterization data, and left ventriculographic findings Thus all 10 cases of tricuspid pouch were proved to belong in Grade II

In addition of those who died of ECD with or without operation in the last 10 years, 38 autopsy specimens were available for this study Tricuspid pouch was found in seven of them (Table II)—an incidence of approximately 18 per cent. Radical correction had been attempted on all seven of these patients, one male and six female, whose ages ranged from five to 33 years A preoperative left ventriculogram had been taken of only two of these seven and tricuspid pouch was observed in both (cases 1 and 2)

Since two of the autopsied cases are included with the clinical cases the total number of patients with tricuspid pouch was 15 In retrospective study, chest x ray films, ECG's, phonocardiograms and cardiac catheterization data were re examined in all 15, but there were

pouch by Baron and his group placed additional emphasis on this phenomenon However only a few reports are available regarding its radiologic appearance among various types of ECD [4,5]

The authors study of its incidence among ECD s of Grades I to III showed 12 per cent by left ventriculography and 18 per cent in autopsy specimens All 15 cases with the tricuspid pouch belonged exclusively to Grade II If these incidence rates were calculated in a group of ECD of Grades I and II only the pouch is found in 20 per cent of cases by left ventriculography and in 26 per cent of the autopsy specimens The fact that the tricuspid pouch is found exclusively in Grade II has an important diagnostic implication In ECD of Grade II the pathologic anatomy consists of ostium primum defect with clefts in the anterior mitral and septal tricuspid leaflets Although the septal leaflet of the tricuspid valve in the majority of cases has a cleft deficiency in leaflet tissue such as maldevelopment in the anterior one third of the septal leaflet was observed in most cases Since all of the tricuspid pouch bulged into the portion where there is a defect in the valvular tissue it is considered that the anterior one third of the cuspid leaflet itself is involved in formation of the tricuspid pouch

Since the number of reports on this subject is extremely limited, further investigation of its etiology is warranted. However it seems reasonable to assume that weak subvalvular tissue consisting of short chordae and thin fibrous tissue[6] swells to the tricuspid side and adheres to the inner surface of the tricuspid valvular tissue under the strong influence of left ventricular pressure As the shape of the tricuspid pouch bears strong similarity to a membranous septal aneurysm [7] it is important to note that in the latter instance the right ventricular surface of the bulge may be covered or attached with short chordae of the tricuspid valve and the structure of the septal leaflet of the tricuspid valve is inherently normal whereas in the former the pouch and the septal leaflet form an inseparable structure It is important to differentiate the membranous septum in the normal heart from an obliterated subvalvular space in ECD in which formation of the membranous septum has never taken place embryologically Therefore if the tricuspid pouch is demonstrated on a left ventriculogram, it indicates the presence of obliterated subvalvular space by subvalvular tissue and the septal tricuspid leaflet and thus the classification of either Grade I or Grade II The possibility of Grade III deformity where the subvalvular space remains wide open is thus excluded. It is important to diagnose the type of ECD by left ventriculography in order to choose the proper surgical procedure



Fig 3 Lateral view in diastole (case 9) Arrow points to tricuspid pouch



Fig 4 Frontal view in diastole (case 9) Arrow points to tricuspid pouch

Determination of Grade I II or III by demonstrating interventricular shunt was dis



Fig 1 Lateral view in systole (case 8) Arrow points to tricuspid pouch



Fig 2 Frontal view in systole (case 8) Arrow points to tricuspid pouch

in four patients—three of medium severity Of these three two died after operation The remaining one showed slight residual left to right shunt at the ventricular communication This was considered negligible at operation because of its small size

Autopsy findings In all seven cases cleft of the anterior mitral leaflet and hypoplasia of the septal leaflet of the tricuspid valve were observed No VSD was found in any specimen All of them belonged in Grade II

In every instance the tricuspid pouch was found in the anterior one third of the septal leaflet of the tricuspid valve (Fig 5) The posterior portion of the septal leaflet was found to be hypoplastic However, this portion of the leaflet had chordae tendineae from the ventricular septum and the papillary muscle whereas at the tricuspid pouch no chordae were found at all

Two cases resembled a lobulated cyst consisting of four to six lobules, four cases were of saccular shape with a smooth contour, in one case the pouch extended sagittally on the ventricular septum protruding slightly toward the right The maximum size found was 1 5 by 1 2 cm and the minimum was 0 5 by 0 4 cm

The thickness of wall differed according to the location from which the measurement was taken The base was thicker, on the average being 1 2 mm the top of the pouch was thinner, averaging 0 7 mm There was no rupture or perforation found in the pouch

The mobility of the saccular tissue was restricted it seemed not to bulge in either systole or diastole

In no case did swelling significantly disturb the tricuspid valvular function

In the left ventricular view, the orifice of the pouch was crossed by several short chordae tendineae which arose directly from the ventricular septum about 1 cm below the right coronary cusp (Fig 6) These chordae crossing the orifice were attached to the anterior mitral leaflet

Since the tricuspid pouch protruded into the inflow tract of the right ventricle, there was no definite obstruction to the outflow due to this protrusion

Discussion

The presence of the tricuspid pouch in autopsy specimens of ECD has already been reported[3] Left ventriculographic demonstration of the

dicates the possibility of Grade II malformation

The pouch resembles membranous septal aneurysm in its etiology and appearance in left ventriculograms However in the majority of cases, it was found that the former protrudes toward the inflow portion while the latter protrudes toward the outflow portion of the right ventricle

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Fig 5 Tricuspid pouch in right side of heart at autopsy (case 1)



Fig 6 Orifice of tricuspid pouch in left side of heart at autopsy (case 1)

cussed However the interventricular shunt is occasionally absent even in Grade III cases[8] Furthermore evaluation of the interventricular shunt becomes difficult in the presence of mitral insufficiency Therefore identification of the tricuspid pouch by left ventriculography is another criterion in the classification of ECD even though its incidence rate is low

The appearance of the tricuspid pouch strongly resembles that of membranous septal aneurysm which is infrequently associated with VSD Differentiation can be made easily since the former bears the characteristic features of ECD such as the goose neck sign or scalloping of the anterior mitral leaflet

The greater part of the membranous septal aneurysm grows in the commissural zone between the septal and anterior leaflets of the tricuspid valve below the crista supraventricularis If the aneurysm attains large size, it may cause stenosis in the outflow tract of the right ventricle[9] in addition to spontaneous rupture and abnormality in cardiac rhythm[10] However, as stated above these were not found in our 15 cases It was our impression during open heart surgery that the tricuspid pouch would not adversely affect right ventricular function Therefore no additional measures were taken to correct the pouch However in cases where the pouch assumes an enormous size leading to stenosis of the tricuspid orifice or when its wall is attenuated which may lead to rupture appropriate corrective measures should be considered

Summary

A tricuspid pouch was found in 15 out of 118 patients with ECD diagnosed either clinically by left ventriculography or at autopsy The incidence demonstrated clinically with left ventriculography was 12 per cent at autopsy, 18 per cent

The pouch is found exclusively in Grade II of ECD Therefore presence of the pouch in the lateral view of a left ventriculogram strongly in

index and stroke output and pulmonary and systemic vascular resistances (in units)

Systolic time intervals were obtained with simultaneous polygraphic recordings of a phonocardiogram carotid arterial pulse and electrocardiogram (ECG) at a paper speed of 100 mm per second The details of this method have been previously described.[11]

The following intervals were calculated (1) pre ejection period (PEP) (2) left ventricular ejection time (LVET) (3) PEP/LVET ratio Pre ejection period index (PEPI) was determined by the following formula PEPI = 0 4 heart rate + PEP Left ventricular ejection time index (LVETI) was obtained by the formula LVETI = 1 6 heart rate (females) or 1 7 heart rate (males) + LVET

Renal studies were performed as follows An indwelling Foley catheter was positioned in the bladder on the morning of the study After complete emptying of the bladder urine was collected continuously for 30 to 45 minutes At the conclusion of each period of drug administration the bladder was emptied by suprapubic pressure Blood samples for renal studies were obtained by means of one of the venous catheters Urine and blood samples were analyzed for electrolyte content and creatinine urine volume was measured for each period of drug infusion Calculations of clearance values were made using standard methods

Thirty to 45 minutes after completion of catheterization procedures hemodynamic renal and noninvasive parameters were recorded under basal conditions Dopamine was administered intravenously by the micro drip technique at infusion rates of 1 5 and 10 μg per kilogram per minute for periods of 30 minutes each Repeat recording of all parameters was accomplished at the end of each dopamine infusion period Statistical analysis and paired tests for significance were applied to all values obtained

Results

The effects of dopamine upon hemodynamic parameters systolic time intervals and renal functions are presented for the group in Table I and graphically expressed in Figs 1 to 4

Cardiac output increased steadily and significantly with progressive doses of the drug up to 87 per cent over control values Maximal effect was reached with an infusion rate of 5 μg per kilogram per minute in four patients and with 10 μg per kilogram per minute in five cases The mean infusion rate at which maximal cardiac output was obtained for the group was 6 9 μg per kilogram per minute Two patients deserve special mention because their cardiac output diminished with the dose of 10 μg per kilogram per minute Both were patients with severe congestive heart failure in functional Class IV secondary to alcoholic cardiomyopathy and to advanced coronary disease respectively This response was associated with a reduction in

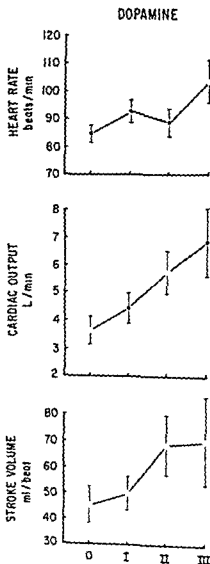


Fig 1 Dose related effects of dopamine on heart rate cardiac output and stroke volume In this and other figures each dose response curve represents the mean values and standard error for the group at a control state (0) and following infusion rates of 1 (I) 5 (II) and 10 μg per kilogram per minute (III)

Dose-related hemodynamic and renal effects of dopamine in congestive heart failure

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A nonglycoside inotropic agent with well defined pharmacologic properties may be of considerable value in the treatment of congestive heart failure and low cardiac output syndrome Although many vasoactive amines are available to the clinician hemodynamic data in man fully characterizing their dose related actions are in complete

Dopamine is a catecholamine with pharmacologic effects that are well suited to the acute management of such patients because it possesses positive inotropic properties and increases renal blood flow [1] At varying dosage levels it may or may not increase total peripheral vascular resistance [2] Most previous studies on this drug have emphasized its pharmacologic effects in the experimental animal [3,4] Clinical investigations have been conducted in normal man[5] and patients with cardiogenic shock [6-9] However, detailed hemodynamic investigations in patients with acute or chronic congestive heart failure are limited

The present investigation was designed to study the dose related effects of dopamine in a group of patients with severe chronic congestive heart failure Hemodynamic and renal parameters were measured during the administration of graded increments of the drug Simultaneously systolic time intervals were recorded to correlate noninvasive with invasive techniques This correlation could be important in assessing the adequacy of catecholamine therapy in clinical situations

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Materials and methods

Nine patients (five men and four women) whose ages ranged from 20 to 61 years were selected for this investigation All had congestive heart failure secondary to myocardial coronary or valvular disease Three patients were in functional Class III and six were in functional Class IV (New York Heart Association Classification) Inotropic or vasoactive agents had been discontinued for 48 hours preceding the study Informed consent was obtained from each patient after proper description of the procedure and its aims

Standard hemodynamic techniques and instrumentation were used Catheters were placed in the superior vena cava and pulmonary artery via antecubital vein cut down or femoral vein puncture An arterial catheter was introduced percutaneously through one of the femoral arteries by means of Seldinger s[10] technique

Pulse pressure curves were obtained with P23DB Statham transducers Cardiac output determinations were carried out in duplicate by dye dilution of indocyanide green or Fick method All tracings were recorded with a PR 12 Electronics for Medicine Hemodynamic measurements consisted of heart rate central venous, pulmonary artery pulmonary wedge and aortic pressures aortic dp/dt cardiac output cardiac

Table I—cont d

Parameter	*Basal*	*1 μg/Kg/min.*	*5 μg/Kg/min.*	*10 μg/Kg/min.*
Pulmonary vascular resistance (units)				
Mean ± S E	3 4 ± 1 3	2 5 ± 0 7	1 5 ± 0 3	2 4 ± 0 8
Per cent	100	74	44	71
P		NS	NS	NS
Central venous pressure (cm. H_2O)				
Mean ± S E	10 ± 2 3	11 ± 2.3	10 ± 2 0	9 0 ± 1 7
Per cent	100	112	99	89
P		NS	NS	NS
Systolic time intervals				
PEPI (msec)				
Mean ± S E	151 ± 7 6	148 ± 6 6	126 ± 5 6	128 ± 9 4
Per cent	100	98	83	85
P		NS	0 01	0 01
LVETI (msec)				
Mean ± S E	376 ± 8 9	375 ± 6 6	381 ± 6 9	380 ± 9 7
Per cent	100	100	101	101
P		NS	NS	NS
Ratio				
Mean ± S E	0 52 ± 0 06	0 51 ± 0 05	0 40 ± 0 04	0 46 ± 0 07
Per cent	100	98	76	88
P		NS	0 01	0 05
Renal functions				
Urine flow (ml /min)				
Mean ± S E	1 5 ± 0 31	2 3 ± 0 63	5.5 ± 1 29	5 0 ± 1 37
Per cent	100	152	361	326
P		NS	0 05	0 05
Na excretion (mEq /min × 10 ^{2})				
Mean ± S E	6 5 ± 3 4	5 1 ± 2 0	9 4 ± 3 5	16 ± 5 6
Per cent	100	79	145	246
P		NS	0 01	0 05
Creatinine clearance (ml./min.)				
Mean ± S E	59 ± 6 0	73 ± 4 7	72 ± 3 6	90 ± 16 4
Per cent	100	124	123	153
P		0 05	0 05	0 05

pressure rise while cardiac output fell This atypical response was observed at an infusion rate of 10 μg per kilogram per minute

Systemic vascular resistance diminished significantly to 35 per cent below base line This effect persisted in seven patients at the infusion rate of 10 μg per kilogram per minute However as indicated above a sharp increase was observed in two cases and consequently the values for the entire group did not achieve significance at the highest dosage level

Pulmonary wedge pressure mean pulmonary pressure pulmonary vascular resistance and central venous pressure were not consistently modified.

Pre-ejection period index diminished to 27 per cent below control values Maximal effect was achieved with 5 μg per kilogram per minute in four patients and with 10 μg per kilogram per minute in five cases A close parallel was observed between PEPI and stroke volume for the group as a whole When examined individually the maximal effect upon stroke volume and PEPI was attained with similar doses in five cases However in four patients maximal responses were not strictly parallel

Left ventricular ejection time index did not change significantly and was in fact stable throughout the study

The *PEP/LVET* ratio paralleled the changes of the pre ejection period.

A striking increase in *urine flow* was observed

Table I Effects of dopamine

Parameter	Basal	1 μg/kg/min	5 μg/kg/min.	10 μg/kg/min.
Hemodynamics				
Heart rate (beats/min.)				
Mean ± S.E.	83 ± 3 3	93 ± 3 7	89 ± 5 1	104 ± 7 9
Per cent	100	112	107	125
P		0 01	NS	0 05
Cardiac output (L /min)				
Mean ± S.E.	3 6 ± 0 5	4 5 ± 0 6	5 8 ± 0 8	6 7 ± 1 3
Per cent	100	126	162	187
P		0 01	0 01	0 05
Cardiac index (L /min./M [2])				
Mean ± S F	2 1 ± 0 3	2 5 ± 0 3	3 4 ± 0 5	3 8 ± 0 8
Per cent	100	122	164	184
P		0 01	0 01	0 05
Stroke volume (ml)				
Mean ± S F	44 ± 6 7	49 ± 5 8	67 ± 11	68 ± 15
Per cent	100	110	153	154
P		NS	0 05	0 05
Mean aortic pressure (mm Hg)				
Mean ± S E	81 ± 5 0	86 ± 4 3	91 ± 5 1	92 ± 6 2
Per cent	100	106	112	114
P		NS	NS	NS
Aortic dp/dt (mm Hg/sec)				
Mean ± S E	771 ± 77	875 ± 93	1 081 ± 126	1 471 ± 141
Per cent	100	114	140	191
P		NS	0 05	0 01
Systemic vascular resistance (units)				
Mean ± S E	24 ± 4 8	18 ± 2 4	16 ± 1 8	17 ± 4 5
Per cent	100	77	65	70
P		0 05	0 05	NS
Pulmonary wedge pressure (mm Hg)				
Mean ± S E	22 ± 2 7	21 ± 2 3	23 ± 2 8	24 ± 4 0
Per cent	100	99	105	113
P		NS	NS	NS
Mean pulmonary pressure (mm Hg)				
Mean ± S E	30 ± 3 3	31 ± 3 2	31 ± 3 6	37 ± 4 7
Per cent	100	102	101	122
P		NS	NS	0 05

stroke volume and an increase in systemic vascular resistance

Stroke volume rose concomitantly with cardiac output to 54 per cent above control values The maximal effect was observed with 5 μg per kilogram per minute in six patients and with 10 μg per kilogram per minute in only three cases The mean infusion rate for optimal effect was 7 μg per kilogram per minute for the group

Heart rate did not change appreciably up to an infusion rate of 5 μg per kilogram per minute A moderate increase in mean values was observed with higher concentration of the drug However in four cases the rate was more than 120 per minute at an infusion rate of 10 μg per kilogram per minute and one of these patients developed a transient nodal tachycardia

Aortic dp/dt was augmented significantly up to 91 per cent above control values This augmentation was progressive to the maximal infusion rate of 10 μg per kilogram per minute in eight of the nine subjects including those who had already attained maximal cardiac output or stroke volume responses

Mean aortic pressure did not change significantly for the group although slight increase paralleled increments in cardiac output In only the two cases mentioned above did mean aortic

output improved up to 32 per cent in both groups. However induced tachycardia was found to be a significant limiting factor

Dopamine shares some of the pharmacologic properties of isoproterenol since both drugs act upon beta adrenergic receptors Studies in the experimental animal[3,4] and normal man[5] have demonstrated augmentation of myocardial con tractility resulting in increased cardiac output stroke volume and left ventricular dp/dt. Mean arterial pressure is essentially unchanged and systemic vascular resistance tends to be reduced On the other hand while isoproterenol is charac terized by tachycardia and predominant vasodilation in skeletal muscle with no signifi cant or proportional increase in renal blood flow[14] dopamine has been reported to have little effect on heart rate and to induce preferential renal vasodilation and vasoconstriction in skeletal muscle particularly at high doses[2]

The present investigation confirms the phar macologic effects of dopamine and demonstrates its clinical applicability in the short term man agement of patients with severe congestive heart failure Direct hemodynamic observations showed significant improvement in cardiac out put cardiac index stroke volume and aortic dp/dt Particularly remarkable was the increment of cardiac output to 87 per cent above control values a result not paralleled by any other available inotropic agent

Information on hemodynamic effects of dopamine in patients with congestive heart failure is scarce Horwitz and associates[5] and McDonald and colleagues[15] reported an increase of 20 to 60 per cent in cardiac output measured in normal man Loeb and co workers[9] observed in crements of 40 per cent in patients with car diogenic shock in fact, most of the reported clini cal experience with dopamine has been in the setting of shock a condition associated with mul tiple variables including effective circulating volume peripheral vascular resistance myocar dial integrity and high mortality rates despite presently available pharmacologic interventions In this context the evaluation of drug action is difficult Rosenblum and associates[16] have re ported hemodynamic and renal effects of dopamine in patients with congestive heart failure utilizing infusion rates up to 6 μg per kilogram per minute They observed a 26 per

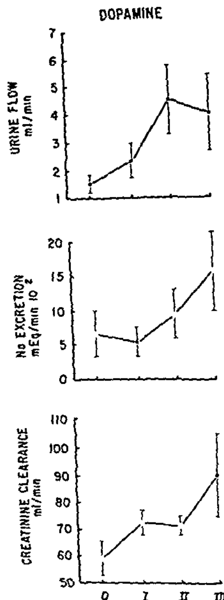


Fig 4 Dose related effects of dopamine on urine flow sodium excretion and creatinin clearance

cent increase in cardiac index but did not estab lish a dose response curve Rosenblum and Frieden[17] have also used dopamine after open heart surgery without direct hemodynamic ob servations

Our results were not associated, in general with inordinate tachycardia and occurred in the context of stable mean aortic pressures and a reduction in systemic vascular resistance cir cumstances favoring vascular perfusion without augmentation of myocardial afterload.

The determination of a dose response curve

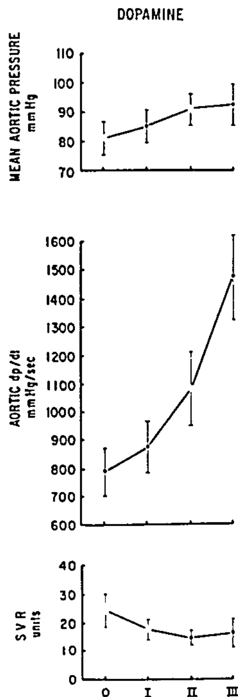


Fig 2 Dose related effects of dopamine on mean aortic pressure aortic dp/dt a d systemic vascular resistance

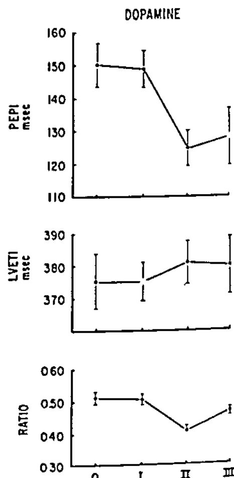


Fig 3 Dose related effects of dopamine on systolic time inter vals pre ejection period index left ventricular ejection time index and their ratio

in eight patients on whom adequate measure ments were obtained Four had maximal responses at 5 and four at 10 μg per kilogram per minute

Sodium excretion was measured in four pa tients A progressive and significant increment in excretion was seen up to an infusion rate of 10 μg per kilogram per minute

Creatinine clearance also measured in four subjects increased 53 per cent above control with an infusion rate of 10 μg per kilogram per minute

Discussion

The use of nonglycoside inotropic agents may be of significant therapeutic value in conditions where the administration of digitalis compounds is controversial or contraindicated Such is the case in patients with myocardial infarction low cardiac output syndrome after cardiac surgery or severe heart failure associated with digitalis intolerance

Catecholamines particularly isoproterenol have been used for this purpose considering their rapid onset of action flexibility of adminis tration and withdrawal and possible combina tion with other modalities of treatment. The hemodynamic effects of isoproterenol were inves tigated by Beregovich and associates[12,13] in two groups of patients presenting with a low cardiac output syndrome or with cardiac failure The first group consisted of 10 patients in the early postoperative period of prosthetic valve replace ment. The second group was made up of 10 pa tients with acute myocardial infarction Cardiac

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with progressive concentrations of the drug permits the conclusion that a dose of 5 μg per kilogram per minute was optimal in terms of over all hemodynamic effects With administration of 10 μg per kilogram per minute three patients developed sinus tachycardia over 120 per minute one patient experienced a transient nodal tachycardia, and two patients sustained paradoxical reductions in cardiac output

Remarkable effects were also observed for urinary output sodium excretion and creatinine clearance Such results are clearly different from those induced by catecholamines with predominant alpha stimulating properties Our data can be contrasted with the action of isoproterenol which induces no significant increase in total renal blood flow and has little effect on sodium excretion Goldberg and associates[18] and McDonald and colleagues[15] have also studied the effects of dopamine in patients with congestive heart failure and observed increased renal blood flow, glomerular filtration rate urine flow and sodium excretion This preferential action of dopamine is due to a direct renal vasodilation as documented in the dog by McNay and associates[19]

A broad though not strict correlation was observed between direct hemodynamic parameters particularly stroke volume and pre ejection period, as measured by systolic time intervals Although these noninvasive" parameters indicated the trend for the group individual variations were difficult to correlate Thus while systolic time intervals may be utilized in assessing the pharmacologic action of inotropic agents in general, the applicability of these techniques to individual patients may be of limited value because the interplays between afterload preload, and inotropic effects of a drug are complex and vary from patient to patient

Our investigation demonstrates that dopamine combines the properties of a potent inotropic agent, capable of improving the performance of the heart as a pump with a selective renal vascular action resulting in increased diuresis and natriuresis The establishment of a dose response curve enables adjustment of the rate of administration to avoid tachycardia arrhythmias or undue vasoconstriction which can occur with excessive dosage

Further experience with this drug in different clinical situations may establish dopamine as a valuable agent in the clinical management of heart failure

Summary

The hemodynamic effects of dopamine were studied in nine patients with congestive heart failure A dose related increase in cardiac output and stroke volume was observed with infusion rates up to 5 μg per kilogram per minute in all patients more rapid infusions resulted in a diminished response in many individuals Tachycardia was significant only at an infusion rate of 10 μg per kilogram per minute Dose related increments in aortic dp/dt, urine flow, sodium excretion, and creatinine clearance were also observed A correlation of invasive and noninvasive techniques for evaluating the hemodynamic effects of dopamine is presented and the potential clinical usefulness of dopamine discussed

Dopamine (Intropin) used in this investigation was kindly supplied by Arnar Stone Laboratories Inc

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The authors gratefully acknowledge the participation of Drs Ralph Schneebaum Ruth Diaz and Ralph D Angelo in this work

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Table I Mean blood pressure (BP) values at admission to study according to smoking class and age

Age group	*Nonsmokers*		*Current cigarette smokers*		*Ex-cigarette smokers*	
	No	*BP (mm. Hg)*	*No.*	*BP (mm. Hg)*	*No*	*BP (mm. Hg)*
Systolic						
34	28	121.9	50	119.3	21	125.3
35 39	35	124.4	35	119.5	36	121.6
40-44	45	123.5	56	119.0	45	120.3
45 49	53	121.8	40	120.2	52	124.5
50 54	26	122.4	21	120.5	47	124.1
55+	45	123.7	12	129.0	43	126.1
Totals, crude	232	123.0	214	120.1	244	123.6
Totals, standardized		122.9		120.1		123.2
Diastolic						
34	28	75.4	50	73.1	21	79.2
35 39	35	78.9	35	75.8	36	76.9
40 44	45	78.1	56	74.6	45	76.9
45 49	53	77.9	40	76.8	52	78.6
50 54	26	76.4	21	74.6	47	77.8
55+	45	76.6	12	77.8	43	75.8
Totals crude	232	77.4	214	75.0	244	77.7
Totals standardized		77.4		75.0		77.8

Standardized on the basis of the age distribution of current cigarette smokers.

to study but were not smoking at entry

(4) quitters—subjects who were smoking cigarettes at entry to study but who had stopped smoking during follow up period.

The subjects ranged in age from 25 to 64 years at the time of the initial examination with a mean age for the total series of 45 years. Mean ages of subjects within smoking classes indicate that current cigarette smokers and quitters were younger on the average (43 and 42 years respectively) than nonsmokers and ex-cigarette smokers (46 and 47 years respectively) The variability in average age among smoking classes requires the age dimension to be included in the analyses of the relationship between smoking class and blood pressure that follow And since changes in body weight appear to affect blood pressure levels this variable will also be included in the analysis

The examination of the data will fall into two main parts (1) a cross sectional view of the characteristics of the subjects at entry into the study according to smoking habits and (2) a longitudinal analysis of the changes in blood pressure for those subjects who modified their smoking habits over the five year follow up period.

Analysis and results

Blood pressure and body weight at admission Table I gives the mean systolic and diastolic blood pressure values at admission according to smoking habits and age classes Current cigarette smokers presented a lower over all mean age standardized systolic pressure (120.1) than nonsmokers (122.9) and former smokers (123.2) Lower over all mean diastolic blood pressure for current cigarette smokers (75.0) than for nonsmokers (77.4) and former smokers (77.8) was also recorded. In every age class but one the blood pressure values of the cigarette smokers were lower than those of the non smokers and former smokers

The body weight values at entry into the study according to smoking class and age are given in Table II From this table it may be seen that ex-cigarette smokers (those who quit cigarette smoking at some time prior to entry into the study) were by far the heaviest in body weight of the smoking classes Ex-cigarette smokers with

Effect of smoking on blood pressure

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The 1971 Public Health Service Report on smoking and health concluded Some epidemiological studies have indicated that smokers tend to have lower mean systolic and/or diastolic blood pressure than nonsmokers while other studies have not found this to be the case [1] In a separate and more extensive review of blood pressure levels according to smoking habits by Larson and Silvette,[2] lower levels of blood pressure among smokers than nonsmokers were indicated in most studies and ex smokers tended to have higher blood pressures than current cigarette smokers Blood pressure differences between smoking and nonsmoking groups have been attributed by some to body weight (adiposity) differentials among the various smoking groups [3]

Most research on the relationship of cigarette smoking to blood pressure is based on cross sectional and prevalence data Longitudinal studies measuring changes in blood pressure over time for subjects with different smoking habits are rare Even less information is available on blood pressure changes for persons who have recently given up smoking cigarettes This study will examine the secular changes in systolic and diastolic blood pressure according to smoking habits over an interval of five years in a series of healthy white veterans

Data and methods

The data on which this report is based were derived from a series of 849 adult white male veterans participating in the Normative Aging Study of the Veterans Administration Outpatient Clinic in Boston Mass —an ongoing prospective study of aging This is a selected population since the participants were rigidly screened for an initial high level of health and for a reasonable expectation of geographical stability to assure their lifetime participation in the investigations [4] Special screening for admission into the study was made with respect to blood pressures [4] Subjects were excluded whose blood pressures in millimeters of mercury were greater than 140 systolic and 90 diastolic Anthropometric and demographic characteristics such as ethnicity, socioeconomic status, and occupation were not used in qualifying subjects for the study

Subjects were examined at entry to the study and approximately five years later Blood pressure measurements were taken by the examining physicians using standardized mercury sphygmomanometers Subjects were seated with their arms resting on a desk Diastolic blood pressures were recorded at the point of disappearance of sounds Body weight values were obtained during the same examinations as blood pressures

The smoking habits of subjects were obtained at examinations by direct interview Subjects with mixed forms of smoking (combinations of cigar, pipe and cigarette) and former or current smokers of cigars or pipe exclusive of cigarettes were excluded from this analysis Of the total 849 available subjects 794 had smoking habits which could be classified into one of the following four classes

(1) nonsmokers—subjects with no history of tobacco smoking at entry to study,
(2) current cigarette smokers—subjects who gave a history of cigarette smoking at entry and at follow up period
(3) ex cigarette smokers—subjects who had a history of cigarette smoking prior to entry

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Table IV Mean weight values (lb) at admission to study and at follow up for continuing cigarette smokers and quitters according to age

Age group	*Continuing cigarette smokers*				*Quitters*			
	No	*Admission*	*Follow up*	*Change*	*No*	*Admission*	*Follow up*	*Change*
34	50	171 4	176 8	+5 4	20	170 1	180 5	+10 4
35 39	35	171 9	176 4	+4 [illegible]	26	176 2	182 3	+6 1
40 44	56	170 0	173.2	+3.2	31	174 8	184 7	+9 9
45 49	40	172 8	176 0	+3 2	9	177 6	184 7	+6 9
50 54	21	167 0	16[illegible] 5	−1.5	11	171 5	177 9	+6 4
55+	12	152 1	153 8	+1 7	7	161 0	162 3	+1.3
Totals *crude*	214	170 0	173 5	+3 5	104	173 2	181 1	+7 9
Totals standardized†		170 0	173 5	+3 5		173 4	181 4	+8 0

p < 0 05
p < 0 01
†Standardized on the basis f age di tribution of the cont nuing cigarette smokers

time of admission to the study who quit smoking at some time during the five year follow up period. This group the quitters represents those subjects who changed their smoking habits and allows for the evaluation of changes in blood pressure with changes in smoking habits viewed in light of concomitant body weight changes Current cigarette smokers at admission to study and at follow up were used as the standard of comparison for the quitter group

Changes in blood pressure of quitters and continuing cigarette smokers by age The data for mean systolic and diastolic blood pressure at admission and follow up for quitters and current cigarette smokers are found in Table III The over all crude and age standardized means of these measures at admission and follow up are given for both groups to indicate the extent of the changes for the total series.

With respect to systolic blood pressure it may be seen that the quitters showed substantial increases in blood pressure for every age class over the follow up period The over all age standardized increase in systolic blood pressure amounted to 4 0 mm Hg this was statistically significant. On the other hand the continuing cigarette smokers systolic blood pressure was unchanged over the same follow up period

Similarly the quitters diastolic blood pressures significantly increased by an average of 2 5 mm Hg over the follow up period in comparison with a modest decline (1 1 mm Hg) for the continuing cigarette smokers.

Changes in body weight of quitters and continuing cigarette smokers by age Concomitant with the above changes in blood pressure both the quitters and the continuing cigarette smokers displayed significant increases in weight over the five year surveillance period (Table IV) The quitters gained on the average a striking eight pounds the continuing cigarette smokers also gained weight (3 5 pounds)—less than one half as much as the quitters It is also to be noted that the younger subjects in each smoking category showed the largest weight increases over the follow up period.

Blood pressure changes by weight change groups and smoking classes A more comprehensive exposition of the relationship between weight change and blood pressure change by smoking class and between systolic and diastolic measures produced the data shown in Table V Weight change categories from admission to follow up have been created to indicate appreciable weight loss (5 to 25 pounds) little or no change (4 to +4 pounds) moderate weight increase (+5 to +12 pounds) a marked weight gain (+13 to +30 pounds)

The most striking result is that giving up

Th extrem ends f the tails of t[illegible] distribution of w ght changes ha e not be n used so as not to unduly effect the trends.

Table II Mean weight values at admission to study according to smoking class and age

Age group	Nonsmokers		Current cigarette smokers		Ex-cigarette smokers	
	No.	wt (lb)	No.	wt (lb)	No.	wt (lb)
34	28	171 0	50	171 4	21	184 1
35 39	3[illegible]	175 9	35	171 9	36	175 4
40 44	45	171 5	56	170 0	45	178 5
45 49	53	172 0	40	172 8	52	177 4
50 54	26	173 6	21	167 0	47	173 3
55+	45	168 4	12	162 1	43	170 1
Totals crude	232	171 8	214	170 0	244	175 8
Totals standardized*		172 2		170 0		178 1

*Standardized on the basis of age distribution of current cigarette smokers

Table III Mean blood pressure values (mm Hg) at admission to study and at follow up for continuing cigarette smokers and quitters according to age

Age group	Continuing cigarette smokers				Quitters			
	No	Admission	Follow up	Change	No	Admission	Follow up	Change
Systolic BP								
34	50	119 3	119 4	+0 2	20	119 4	119 8	+0 6
35 39	35	119 5	118 9	-0 5	26	119 9	122 1	+2 2
40 44	56	119 0	118 7	-0 2	31	121 4	125 9	+4 5
45 49	40	120 2	123 1	+2 9	9	125 4	134 0	+8 6
50 54	21	120 5	117 8	-2 7	11	122 2	126 3	+4 1
55+	12	129 0	124 5	-4 5	7	125 7	132 6	+6 9
Totals crude	214	120 1	120 0	-0 1	104	121 4	125 0	+3 6
Totals standardized†		120 1	120 0	-0 1		121 8	125 8	+4 0
Diastolic BP								
34	50	73 1	72 5	-0 6	20	74 0	76 7	+2 7
35 39	35	75 8	73 5	-2 3	26	76 2	77 3	+1 1
40 44	56	74 6	75 2	+0 6	31	76 9	78 6	+1 7
45 49	40	76 8	76 2	-0 6	9	74 4	78 9	+4 5
50 54	21	74 6	71 2	-3 4	11	76 2	79 9	+3 7
55+	12	77 8	72 5	-5 3	7	77 7	77 1	-0 6
Totals crude	214	75 0	73 9	-1 1	104	75 9	78 0	+2 1
Totals standardized†		75 0	73 9	-1 1		75 6	78 1	+2 5

*$p < 0.05$
†Standardized on the basis of age distribution of continuing cigarette smokers

an age standardized mean value of 178 1 pounds were on the average almost six pounds heavier than nonsmokers and about eight pounds heavier than current cigarette smokers The latter group of smokers were somewhat more than two pounds lighter in body weight than the nonsmokers

Changes in blood pressure and body weight at five year follow up There were 104 subjects classified as current cigarette smokers at the

Table VI Frequency of subjects with hypertension (variously defined, at follow up for current cigarette smokers and quitters

	Current cigarette smokers		Quitters	
	No	%	No	%
Systolic blood pressure 150+	6	2 8	9	8 7
Systolic blood pressure 160+	2	0 9	5	4 8
Diastolic blood pressure 95+	3	1 4	5	4 8

period. Systolic blood pressure levels of 150 and higher were reached by three per cent of the continuing cigarette smokers in contrast to about nine per cent for the quitters Similarly with respect to diastolic blood pressure levels of 95 and over almost five per cent of the quitters were found with these critical levels over the follow up period, as against only 1 4 per cent among the continuing cigarette smokers It is notable that the greatest increase in pressure to hypertensive levels among the quitters has occurred *despite* the fact that this group is younger than the continuing smokers

Discussion

The results presented focused primarily on the smoking issue with age and body weight being controlled in the analysis The findings of lower mean blood pressure and body weight values at time of admission to the study for the current cigarette smokers, as compared with nonsmokers and former smokers were consistent with most studies reported in the literature

Investigation of the influence of changes in smoking habits on blood pressure over a five year period shows clearly that the blood pressure trends of quitters differed from those of continuing cigarette smokers Recent quitters displayed significant increases in systolic blood pressure in all categories of weight change whereas the continuing smokers were declining in pressure with losses of weight and showing increases in pressure with gains in weight In those instances of increasing weight over the surveillance period, greater blood pressure gains were shown by the quitters than the continuing cigarette smokers

With respect to diastolic pressure the quitters exhibited higher pressure values over the five year interval when associated with weight gain but there was virtually no change in blood pressure for the quitters who lost substantial amounts of body weight The continuing cigarette smokers on the other hand, showed a drop in diastolic pressure with weight loss and essentially no change with weight gain

These data suggest that cigarette smoking *tends to have an inhibiting effect* on blood pressure with minimal pressure rises even in instances of substantial weight gains. When this inhibiting effect of cigarette smoking is removed, as in the case of the quitters sharp rises in blood pressure are evident This view receives further support from our finding that the risk of attaining hypertensive blood pressure levels over a five year span is far less pronounced among the subjects who continue to smoke than in those who have recently quit the habit. Thus, the effect of smoking remains after controlling for weight changes

It is possible that developing hypertension may be responsible in some quitters, for decisions to lose weight. In these circumstances loss of weight may be the reaction to this developing hypertension However it would seem likely overall, that the stopping of cigarette smoking is directly related to increase in blood pressure even among those who have lost considerable weight. Unfortunately the data do not allow for the determination of the degree of blood pressure changes according to recentness of giving up cigarettes Further investigation on this point is necessary

Table V Blood pressure changes (mm Hg) at follow up for continuing smokers and quitters according to weight changes and standardized for age*

Smoking class	No	25 to 5	No	-4 to +4	No	+5 to +12	No	+13 to +30
	Weight change (lb.)							
Mean systolic BP changes								
Continuing smokers	32	−4 00	84	−1 52	71	2 85	24	1 50
Quitters	13	1 77	27	2.22	27	4 04	32	3 69
Mean diastolic BP changes								
Continuing smokers	32	−3 28	84	−2 04	71	0 73	24	−0 04
Quitters	13	−0 31	27	−1 96	27	4 30	32	3 94

*Standardized on basis of age distribution of current cigarette smokers

cigarette smoking (quitters) produced increases in systolic blood pressure even in the group that lost an appreciable amount of weight from 5 to 25 pounds The largest increases in systolic blood pressure occurred in those quitters with the largest weight gain the smallest increase among those who lost the most weight This finding is not in evidence in the case of the diastolic blood pressure In this instance, while there were increases in diastolic pressure with increases in weight among the quitters decreases in pressure occur for those quitters who lost weight.

In contrast to the findings for the quitters Table V indicates that continuing cigarette smokers displayed increases in systolic pressure with increases in weight and decreases with decreases in weight With respect to diastolic pressure changes among the cigarette smokers it is significant to note that continuing to smoke over the follow up period appeared to inhibit an increase in pressure even in those who gained considerable weight Declines in diastolic pressure accompanied sharp declines in body weight

Since the blood pressure changes in Table V are all age standardized values it would appear that controlling for age did not affect the singularity of the pressure changes for the cigarette quitters While for the continuing cigarette smokers systolic and diastolic changes were quite consistent with the direction of weight changes in the case of the quitters systolic blood pressure increased with weight loss as well as weight gain With respect to diastolic pressure, there was virtually no change for the quitters, who lost between five and 25 pounds, compared to a mean decrease of 3 3 mm Hg for the continuing cigarette smokers with this substantial weight loss. The quitters who gained weight increased their blood pressure more than did the continuing cigarette smokers

Changes to critical blood pressure levels by smoking class Some of the blood pressure changes seen in the quitters and the continuing cigarette smokers were quite modest and some were fairly substantial Whether or not they were of biological significance is difficult to judge from these over all values Some light might be shed on this area by the following analysis

The rigid screening process insured that all subjects at entry into the study had systolic and diastolic pressures no greater than 140 and 90 respectively During the follow up period a number of subjects had increased their blood pressure levels to critical levels of hypertension Table VI shows the frequency of subjects for quitters and continuing cigarette smokers, whose blood pressure levels had risen to variously defined critical levels of hypertension It is clear from this table that the combined effects of giving up cigarettes and the over all gain in weight produced far greater risks of critical levels of hypertension than continuing to smoke cigarettes. While fewer than one per cent of the continuing cigarette smokers reached systolic blood pressure levels above 160, almost five per cent of the quitters attained this critical level over the follow up

Coronary artery calcification Clinical implications and angiographic correlates

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The association of coronary artery calcification and arteriosclerotic heart disease has been noted by many workers [1-10] These investigators have either utilized postmortem material[1-5] or fluoroscopic screening of patients [6-10] No study available in the literature relates the presence of coronary artery calcification with coronary angiography in the same patients The use of im age intensification and selective coronary angiograms permits precise identification and location of coronary artery calcification and defines the presence of significant coronary ar tery disease Previous fluoroscopic studies have depended on clinical evidence in presuming the presence of coronary artery disease in the ab sence of objective angiographic documentation It is well appreciated that some patients with angina pectoris may have normal coronary ar teries [11,12] Furthermore patients with atypical chest pain or no chest pain may have significant coronary artery disease [12] The purpose of the present report is to compare 250 consecutive pa tients who had arteriosclerotic heart disease with 250 patients without coronary artery disease as defined in all cases by selective coronary angiography By such a comparison the clinical significance of coronary artery calcification will be evaluated.

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Material and methods

In a prospective study 250 consecutive pa tients referred because of angina pectoris and having angiographic evidence of coronary artery disease were compared with 250 consecutive pa tients found at cardiac catheterization to have normal coronary angiograms Excluded from the latter group were patients with aortic valve calcification because such calcification when present, made it difficult to identify with certain ty the presence of coronary artery calcification All patients had complete clinical and hemodynamic evaluation as previously described [13] Calcification was looked for in the vicinity of the coronary arteries in multiple pro jections immediately prior to performing selec tive coronary angiograms After the presence of any calcification had been noted, selective coro nary angiograms were performed by the methods of Sones and Shirey[14] or Judkins [15] In this man ner the location of the calcification in the coro- nary artery was confirmed Cine films were taken in each projection before and during opacifica tion of the coronary arteries in order to confirm exactly the presence and location of the calcifica tion It was sometimes difficult to decide whether calcification was localized to the main left coro nary artery or extended into the left anterior descending artery These two vessels therefore were combined in the presentation Single dou ble or triple vessel diseases were defined as greater than 50 per cent narrowing of one two or three coronary arteries respectively [13] The x ray equipment utilized for this study included a dual field six inch 3 000 gain nine inch 6 000 gain image intensifier system (General Electric) with a 35 mm (Photomechanism) synchronous

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Table II Relationship between coronary artery calcification and the extent and severity of coronary artery disease

	No	No with calcification	Per cent
Number of vessels involved			
Single vessel disease	52	29	56
Double vessel disease	98	75	77
Triple vessel disease	100	86	86
Coronary artery disease with			
Less than 50 per cent narrowing	200	32	16
50 to 95 per cent stenosis	339	155	46
Complete obstruction	211	101	48
Main left coronary disease			
30 per cent to less than 50 per cent narrowing	10	7	70
50 to 95 per cent stenosis	19	15	79
Complete obstruction	1	0	0

in the frequency of coronary artery calcification (46 vs 48 per cent) Thirty patients had disease of the main left coronary artery As indicated in Table II there was no relationship between the severity of disease and the frequency of calcification One patient with complete obstruction of the main left coronary artery had no coronary artery calcification

In the 190 patients with arteriosclerotic heart disease and coronary artery calcification 183 had calcification of the left anterior descending artery while the circumflex and right coronary arteries were calcified in 47 and 59 patients respectively Isolated calcification of the right coronary artery was noted in six patients and the circumflex artery in one Calcification present in only one vessel was not related to the number of vessels involved (Table III) whereas of 70 patients with demonstrated calcification of two or three vessels only three had single vessel coronary artery disease In 54 patients with normal coronary angiograms and coronary artery calcification the left anterior descending artery was calcified in all. Twelve patients had calcification in two vessels and one in all three major coronary arteries Generally the location of the coronary artery calcification was the same whether coronary artery disease was present or absent. Left coronary artery calcification was located at the proximal part of the artery whereas the right coronary artery was calcified anywhere in its course but always proximal to the posterior descending artery

Review of the clinical material on the patients with arteriosclerotic heart disease revealed no relationship between the presence of coronary artery calcification and the duration of symptoms prior myocardial infarction or the presence of hypertension or diabetes mellitus.

Discussion

The results of the present study confirm those of other workers[1-10] of the common finding of coronary artery calcification in patients with arteriosclerotic heart disease In the present study 76 per cent of the patients with arteriosclerotic heart disease had coronary artery calcification In other studies the frequency of coronary artery calcification in patients with arteriosclerotic heart disease varied from 50[9] to 93 per cent[4] In the former study the diagnosis was made on clinical findings and in the later study on postmortem examination The usefulness of finding coronary artery calcification is limited because 22 per cent of the patients with normal coronary angiograms also had coronary artery calcification In their study Oliver and coworkers[9] showed that 24 per cent of their patients with no clinical evidence of arteriosclerotic heart disease had coronary artery calcification whereas the pathologic study of Eggen and associates[4] revealed that 50 per cent of their patients

Table I Relation between coronary artery calcification and age and sex (normal coronary angiogram vs arteriosclerotic heart disease)

Age group (yr)	*Total*			*Male*			*Female*		
	No	*With calcification*		*No*	*With calcification*		*No*	*With calcification*	
		No	%		*No*	%		*No*	%
Normal coronary angiogram									
30 39	41	1	2	18	1	6	23	0	0
40 49	68	5	7	30	3	10	38	2	5
50 59	84	19	23	32	9	28	52	10	19
60 69	47	20	43	20	9	45	27	11	41
70 and over	10	9	90	5	5	100	5	4	80
Total	250	54	22	105	27	26	145	27	19
Arteriosclerotic heart disease									
30 39	16	6	37	14	5	36	2	1	50
40 49	57	37	65	53	33	62	4	4	100
50 59	117	94	80	103	83	81	14	11	79
60 69	52	46	88	43	37	86	9	9	100
70 and over	8	7	88	6	6	100	2	1	50
Total	250	190	76	219	164	75	31	26	84

camera utilizing a grid control x ray tube The cine films were taken at 80 KVP and 50 ma with a 4 msec pulse width at 60 frames per second Statistical analysis was carried out by standard methods[16] with the use of a programmed digital computer

Results

Coronary artery calcification was present in 54 patients (22 per cent) with normal coronary angiograms as compared to 190 patients (76 per cent) with arteriosclerotic heart disease ($p < 0\ 01$) In both groups of patients (Table I) there was a progressive increase in the frequency of coronary artery calcification with increasing age There was no significant difference when comparing patients over 70, whereas in all the other age groups at each decade studied (Table I) there was a significantly ($p < 0\ 01$) greater frequency of coronary artery calcification in the patients with coronary artery disease This was especially evident in the patients below 60 years of age This relation between age and the frequency of coronary artery calcification was not affected by the sex of the patients, except for female patients who had arteriosclerotic heart disease (Table I), in whom the frequency fluctuated between 50 and 100 per cent and was not related to the age groups of the patients

The relationship between coronary artery calcification and the extent and severity of the coronary artery disease is shown in Table II In 52 patients with single vessel disease 29 (56 per cent) had coronary artery calcification, whereas of 198 patients with double and triple vessel disease, coronary artery calcification was demonstrated in 161 ($p < 0\ 01$) However, the frequency of coronary artery calcification in 98 patients with double vessel disease was not different from that of 100 patients with triple vessel disease In 200 coronary arteries with less than 50 per cent narrowing only 32 (16 per cent) of vessels demonstrated coronary artery calcification whereas the 550 vessels demonstrating greater than 50 per cent narrowing revealed 256 (47 per cent) with coronary artery calcification ($p < 0\ 01$) A comparison of the 550 vessels having significant coronary artery disease on the basis of stenosis (50 to 95 per cent stenosis) and complete obstruction revealed (Table II) no significant differences

the main left coronary artery had no calcification Lavine and co workers[18] suggested that calcifications of the main left coronary artery may be useful with other parameters in predicting ahead of time significant left main coronary artery disease This has not been our experience Our findings confirming those of others [2,4,5,10] indicate that the left main coronary and the left anterior descending arteries are the vessels most frequently involved with coronary artery calcification We have found that obtaining the number of vessels involved with calcification is useful in predicting the extent of the coronary artery disease (Table III) Calcification of one vessel was not helpful Calcification of two or three vessels however indicates a low probability that the patient has single vessel disease Of the 42 patients with calcification of two vessels only three patients had significant single vessel disease only while the rest had double or triple vessel disease Similarly no patient with calcification of three coronary arteries had single vessel disease

Attempts to relate the presence of calcification with the duration of symptoms, prior myocardial infarction or the presence of hypertension or diabetes mellitus was not successful. Oliver and colleagues[9] however in their pathologic study did find coronary artery calcification more frequent in patients with hypertension whereas Frink and co workers[1] noted no relationship between coronary artery calcification and hypertension or prior myocardial infarction

Summary

A prospective study of 250 consecutive patients with angiographically proved arteriosclerotic heart disease and 250 consecutive patients with normal coronary angiograms is reported to evaluate the significance of coronary artery calcification Coronary artery calcification was present in 76 per cent of the patients with arteriosclerotic heart disease as compared to 22 per cent of the patients with normal coronary angiograms. The frequency of coronary artery calcification increased progressively with increasing age In patients aged 49 or less the presence of coronary artery calcification strongly favors the diagnosis of arteriosclerotic heart disease Patients with double or triple vessel disease are more likely to have coronary artery calcification than are patients with single vessel disease Calcification was more likely to involve a coronary artery involved with significant disease but was not related to the severity of that disease Calcification of the main left coronary artery was not helpful in predicting significant disease of the main left coronary artery Calcification of two or three coronary arteries indicated that single vessel coronary artery disease was unlikely

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Table III Relationship between the number of vessels with calcification and the number of vessels with significant coronary artery disease

No. of vessels with calcification	No of patients	Single vessel disease	Double vessel disease	Triple vessel disease
1	120	26	46	48
2	42	3	15	24
3	28	0	14	14

with patent coronary arteries had coronary calcification If one considers the age of the patient, the finding of coronary artery calcification can be of value in confirming the presence of coronary artery disease As noted in this study (Table I) and others [1,4,5,7,9] the frequency of coronary artery calcification was directly related to the age of the patient Such a relationship was noted in patients with normal coronary angiograms as well as those with arteriosclerotic heart disease Over the age of 70 the frequency of coronary artery disease in both groups of patients approaches 100 per cent. As noted in Table I, however between the ages of 30 and 59 the finding of coronary artery calcification could have significant value for making the diagnosis of arteriosclerotic heart disease This was especially true for both male and female patients between the ages of 30 to 49 In this age group the frequency of coronary artery calcification in patients with normal coronary angiograms varied from two to seven per cent whereas in patients with arteriosclerotic heart disease the frequency of coronary artery calcification varied from 37 to 65 per cent We therefore agree with others[4,9] on the diagnostic value of coronary artery calcification in the younger age group

In young adults coronary artery calcification is usually limited to the internal elastic membrane associated with degenerative finding of elastic fibers and early atheromatous changes [17] The finding of coronary artery calcification in patients with normal coronary angiograms may thus indicate early atheromatous changes not apparent on selective coronary angiography This is furthermore supported by the observation in such patients that the location of the calcification is similar to that of atheromatous lesions observed on selective coronary angiography [13]

The presence of coronary artery calcification in a patient with clinical evidence of arteriosclerotic heart disease has limited value in predicting the extent and severity of the coronary artery disease (Table II) Although the frequency of coronary artery calcification was significantly greater in patients with double or triple vessel disease as compared to the patients with single vessel disease it should be realized that 56 per cent of the patients with angiographic evidence of single vessel disease had coronary artery calcification Furthermore no significant differences were noted in the incidence of coronary artery calcification when comparing patients with double and triple vessel disease If one next compares coronary arteries demonstrating stenosis (50 to 95 per cent narrowing) with those vessels demonstrating complete obstruction there was no difference in the frequency of coronary artery calcification The only useful aspect of finding coronary artery calcification in a patient with clinical arteriosclerosis was that calcification was more likely to be present in a vessel that also had significant coronary artery disease (Table II) Thus the finding of calcification in the area of the left anterior descending artery in a patient with arteriosclerotic heart disease would strongly favor significant disease of that vessel It would not, however rule out significant disease in another vessel It was interesting that coronary artery calcification of the main left coronary artery in no way predicted significant disease of the main left coronary artery The frequency of coronary artery calcification of the main left coronary artery in patients with 30 to less than 50 per cent narrowing was similar to that found in patients with significant main left coronary artery disease One patient with complete obstruction of

Abnormal atrial activity in lipomatous hypertrophy of the interatrial septum

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With advancing age it seems that atrial arrhythmias occur more frequently [1,3] Some changes within the heart itself are also related to the age of the patient. Collagen content of the myocardium[4] and of the sinoatrial node and internodal tracts[3,5] as well as the amount of fat in the epicardium and the interatrial septum[6,7] increase with age Furthermore amyloid is also more frequently found in the hearts of older patients[8] It has therefore been proposed that these structural changes singly or in combination might be related to the increased incidence of atrial arrhythmias in elderly patients [3,5]

In 1964 Prior[9] described five cases with extreme fat content within the interatrial septum He named this lesion lipomatous hypertrophy of cardiac interatrial septum and believed it not to be a true lipomatous tumor Since then additional cases have been reported [7,10,11] Page[7] described another 10 cases retrospectively collected from necropsy material and Hutter and Page[12] also studied atrial arrhythmias in these patients

Lipomatous hypertrophy of the interatrial septum hitherto only described from the United States of America probably occurs mainly in older patients and might be only an extreme collection of normal fat[6] which in some cases might be the cause of atrial arrhythmias

This prospective study was performed to study the incidence and concomitant electrocardiographic (ECG) changes of lipomatous hypertrophy in 445 consecutive necropsies

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Patients and methods

The necropsies were performed in three Stockholm hospitals caring for aged chronically sick patients. At necropsy the heart was examined with special attention devoted to the interatrial septum. Five cases with extreme fat content of the interatrial septum were thus found. The clinical information was collected from the records and 12 lead ECG s were available in all patients Material for microscopic examination was taken from the interatrial septum in all cases The blocks were stained routinely with van Gieson and hematoxylin and eosin

Results

Clinical findings Some clinical findings are summarized in Table I The youngest patient was 77 and the oldest 84 years of age There were three men and two women Three patients had a history of acute myocardial infarction and hypertension Two of these patients also had a history of congestive heart failure

ECG changes The atrial arrhythmias and P wave changes are given in Table I Two patients had atrial fibrillation In one patient (case 2) this was known to have existed for some years before the present illness In the other patient (case 4) atrial fibrillation was seen on ECG s from four years before and had probably been present for 10 years before the present illness

In two patients a pathological P vector was present with negative P waves in Leads II III and aV_F (Figs 1 and 2) The P wave widths were within normal limits and the P R intervals were 0 13 sec (case 1) and 0 14 sec (case 3) respectively Both patients had biphasic P waves in the right precordial leads In case 1 an ECG was recorded nine years before as well as six months before the present illness On the latter recording

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Fig 5 Typical changes in the interatrial septum of lipomatous hypertrophy (case 1) Section made anterior to the foramen ovale

Table I Clinical findings in five patients with lipomatous hypertrophy of the interatrial septum

Case No	*Age*	*Sex*	*History*	*Atrial arrhythmias*
1	81	M		Negative P waves in Leads II III and aV_F
2	81	M	CHF AMI hypertension pulmonary embolus 15 years earlier	Atrial fibrillation
3	83	F	Left sided hemiplegia	Negative P waves in Leads II III and aV_F
4	84	F	CHF AMI hypertension	Atrial fibrillation
5	77	M	AMI hypertension	Wandering atrial pacemaker

CHF Congestive heart failure AMI acute myocardial infarction

considered the main cause of death in three patients However in two of these patients old or fresh myocardial infarction was found as well The heart was enlarged in all three patients with myocardial infarction In none of the hearts were signs of right ventricular hypertrophy seen In all hearts a massive thickening of the interatrial septum anterior to the foramen ovale with some bulging of the wall was found (Fig 5) The thickness of the septum was in all cases more than 20 mm and the tissue was yellowish suggesting fat

Microscopic findings In all patients except one (case 1) the tissue in the interatrial septum was composed of mature fat cells and some fibrosis was also found interstitially In case 1 there was a mixture of mature fat cells and multilobular fat cells (Fig 6) In one patient (case 2) there were also small areas of amyloid both in the atrium and in the left ventricular wall The muscle cells dispersed in the fatty tissue showed variation in

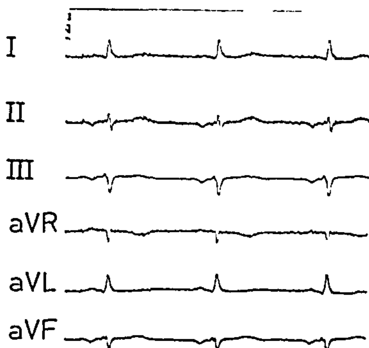


Fig 1 ECG in case 1 showing negative P waves in Leads II III and aV_F

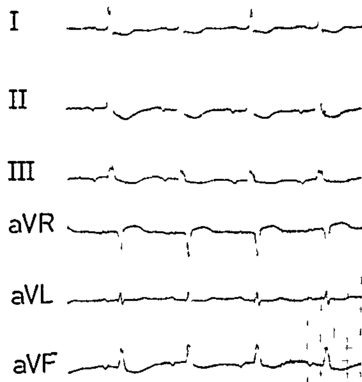


Fig 2 ECG in case 3 showing negative P waves in Leads II III and aV_F

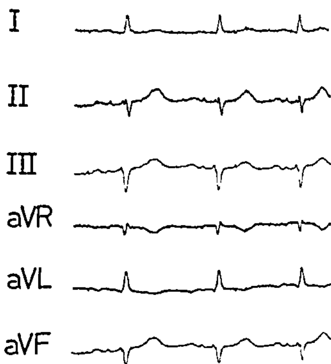


Fig 3 ECG in case 1 six months before the present illness showing widened (0 13 sec) notched P waves

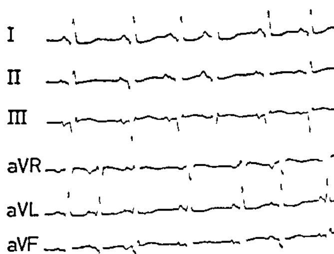


Fig 4 ECG in case 5 showing multiformed P waves with a varying P R interval suggesting a wandering atrial pacemaker Note the dome and dip P wave in Leads III and aV_F

a P R interval of 0 18 sec and widened (0 13 sec) notched P waves were seen (Fig 3) In case 3 a normal ECG was recorded six years before the present illness In one patient (case 5) multiformed P waves were seen with a changing P R interval suggesting a wandering atrial pacemaker (Fig 4) In this patient a normal ECG was recorded nine years before the present illness and an ECG recorded one month earlier showed a normal P vector and supraventricular ectopic beats In the left precordial leads nonspecific ST T changes were seen in four patients

Necropsy findings The findings at necropsy are summarized in Table II One patient died of acute myocardial infarction and another of cerebrovascular disease A malignant tumor was

(case 1) In the other patient (case 3) the sole ECG during the terminal illness showed this P wave configuration

The existence of three preferential internodal pathways in man seems well documented[14] and it has been suggested that damage to these path ways might give rise to changes in P wave con figuration or polarity [14,15] The pathological P vec tor in cases 1 and 3 might represent interatrial conduction disturbances depending on a block in the anterior and middle internodal pathways caused by the extreme fat accumulation anterior to the foramen ovale where these tracts are known to pass [14,16]

It is known that endocardial pacing from the caudal region of the right atrium in man gives rise to a similar pathological P vector usually with a P R interval below 0 12 sec [17] Stimulation in the Eustachian ridge area (posterior interno dal tract) of the dog also produces negative P waves in Leads II III and aV_F.[14] The same P vec tor might possibly arise if the posterior in teratrial pathway is intact with a concomitant block in the two other pathways However if the described P wave changes were caused by in teratrial conduction disturbances one might probably expect a P wave width beyond the usual 0 10 to 0 11 sec [1] and this was in fact seen on a previous ECG in case 1 (Fig 3)

A shift of pacemaker site giving rise to the pathological P vector in cases 1 and 3 cannot be excluded. A P R interval below 0 12 sec and a heart rate between 30 and 60 b p m would be ex pected if the pacemaker site was located in the A V nodal area [1] The heart rate in cases 1 and 3 were 70 and 115 b p m. respectively A coronary sinus rhythm gives rise to negative P waves in Leads II III and aV_F, usually with a P R interval of 0 12 to 0 15 sec [1] and this fits well with the findings in cases 1 and 3 However Moore and as sociates[15] did not find an inverted P wave in Leads II III and aV_F when pacing from the coro nary sinus or A V nodal area in the dog unless there was a concomitant damage to atrial myocardium They proposed that when the P wave is inverted in these leads one should sus pect that intra or interatrial conduction defects coexist with ectopic or retrograde activation of the atria The described P wave changes in cases 1 and 3 might thus be caused by blocking of in teratrial pathways a shift of pacemaker site within the atria or both

When discussing the etiology of the described atrial arrhythmias other causes than lipomatous hypertrophy of the interatrial septum must be considered. Both patients with atrial fibrillation had a history of hypertension and ischemic heart disease These conditions alone[18] could be the cause of the atrial fibrillation and the concomi tant lipomatous hypertrophy of the interatrial septum might be insignificant. In the two pa tients with negative P waves in Leads II III and aV_F, slight arteriosclerosis was found in the coro nary vessels and one of them showed myocar dial fibrosis The cause of the P wave changes in these latter cases is more probably the lipomatous hypertrophy of the interatrial sep tum The patient with wandering atrial pace maker had severe coronary arteriosclerosis hy pertension and old and fresh myocardial infarc tion These findings might also be the cause of the atrial arrhythmia. The dome and dip P wave present in this case has been described in other cases in lipomatous hypertrophy of the in teratrial septum[12] and similar changes have been described in atherosclerotic heart disease [19]

The clinical significance of lipomatous hy pertrophy of the interatrial septum is at present hard to evaluate The lesion is not common and evidently difficult to diagnose in vivo However the lesion might be suspected in elderly patients with atrial arrhythmias where other usual causative conditions are absent

Summary

Five cases of lipomatous hypertrophy of the in teratrial septum were found in a prospective study of 445 necropsies. All five patients had ab normal atrial activity Two patients had atrial fibrillation one patient had a wandering atrial pacemaker and two patients had a pathological P vector with negative P waves in Leads II III and aV_F The changes seen in the latter three cases might be caused by interatrial conduction disturbances shift of pacemaker site or both

The author wishes to thank Andreas Sjögren M D for cri ticizing the manuscript and Hans Nordenstam M D for pro viding the microphotograph.

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Table II Necropsy findings in five patients with lipomatous hypertrophy of the interatrial septum

Case No	Main cause of death	Heart weight (Gm)	Coronary arteriosclerosis	Miscellaneous
1	Esophageal cancer	350	Slight	Myocardial fibrosis
2	Prostate cancer	490	Moderate	Emphysema old anterior myocardial infarction and myocardial fibrosis focal amyloid in atrial and left ventricular myocardium
3	Cerebrovascular disease	360	Slight	Calcification in the mitral annulus
4	Acute myocardial infarction	445	Severe	Old inferior and fresh anterior subendocardial infarction partially patent foramen ovale (diameter 2 mm)
5	Lung cancer	535	Severe	Old diffuse and multiple small fresh inferior myocardial infarctions



Fig 6 Multilobular and mature fat cells within the interatrial septum surrounding a muscle fiber (case 1) (Hematoxylin and eosin × 150)

the shape and size of the muscle nuclei No capsule surrounding this lipid lesion was found in any of the patients and no inflammatory cells were seen In none of the patients with malignant tumor was metastatic cancer infiltration seen within the interatrial septum

Discussion

The gross and microscopic changes in the described five patients fit well with the description of lipomatous hypertrophy of the interatrial septum by other authors [7 9 11]

Prior s[9] five patients were between 66 and 78 years of age and the 10 patients of Page[7] were all more than 69 years old One patient described by Kluge[11] was 64 years old and one patient reported by Okel[10] was 33 years old This latter patient also had a Wolff Parkinson White syndrome and myocarditis Thus of 22 described patients all but two were older than 66 years of age showing that this lesion is most often found in the elderly The present study is hard to evaluate from this point of view since the patients are collected from a necropsy material composed of mainly old patients

All patients of Hutter and Page[12] had atrial arrhythmias They also noted a specific P wave change the ' dome and dip in five of their patients. A similar P wave configuration was seen in the present study in case 5 in Leads III and aV_F (Fig 4) A dome and dip configuration might be explained by an activation of the right atrium from the sinus node down while the left atrium is then activated in an ascending direction from the A V nodal region The possibility of an interatrial block as the cause of the dome and dip P wave was proposed by Hutter and Page [12]

Brody and associates[13] considered three possible mechanisms for P wave changes i e (1) translocation of pacemaker locus (2) variation of exit sites from the sinus node itself and (3) temporary gain or loss of dominance in atrial preferential pathways and this was also pointed out by James and Sherf [14] Any of these mechanisms might be responsible for the change in P wave configuration in the described cases In one of the two patients with negative P waves in Leads II, III and aVF several ECG s recorded at different times showed the same changes and the P wave configuration was thus probably constant

Systolic murmur following myocardial infarction

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The appearance of a murmur following acute myocardial infarction is not an uncommon occurrence. The differential considerations include papillary muscle dysfunction or rupture, perforation of the interventricular septum, and left ventricular dilatation with resultant mitral regurgitation. The clinical course, prognosis, and treatment may differ greatly with each of these entities and therefore the clinician should be familiar with their features if he is to distinguish them. It has been our experience that, contrary to general belief, the clinical picture frequently does not allow the distinction to be made with confidence. This discussion will review the clinical aspects of the causes of a newly discovered murmur after myocardial infarction and present the cases of four patients recently seen at the University of Colorado Medical Center that bear upon the problems in differential diagnosis.

I. Papillary muscle dysfunction

The papillary muscles are exquisitely sensitive to ischemia because of their tenuous blood supply.[14] This is primarily due to the increasing pressure gradient from epicardium to endocardium which lowers subendocardial perfusion.[12] A high incidence of papillary muscle involvement in myocardial infarction should therefore be expected.

Although it has been recognized earlier, papillary muscle dysfunction was not widely accepted as a clinical syndrome until Burch and associates' 1963 article.[4,6] The original concept of the murmur being mid or late systolic[5] was later modified to include holosystolic as well, depending on the functional state and degree of fibrosis of the papillary muscle.[9,12,19,37]

The murmur often appears very early in the course of an infarction; in Heikkila's[19] series of 210 patients it was usually in the first five days. The murmur tends to vary from day to day and in two thirds of the cases it is only Grade 1-2/6 in intensity and may be easily missed. There is a poor correlation between the intensity of the murmur and the severity of the mitral regurgitation due to the depressed ventricular function consequent to the infarction.[19] The murmur is usually located near the apex but if the posterior leaflet is predominantly affected, it may radiate toward the base and simulate aortic stenosis. This is more commonly present, however, in rupture of the chordae tendineae.[15] The character of the murmur has been variably described in different reports ranging from early to mid or late systolic to holosystolic (Table I). It is often transient; it disappeared during hospitalization in 13 per cent and in the next few months in an additional 17 per cent of 117 patients.[19] A fourth heart sound is frequently noted[9,37] and Cheng[9] has described a loud first heart sound in 70 per cent of his patients.

A mid systolic click may occasionally initiate the murmur of papillary muscle dysfunction. This has only been recently appreciated[23] and as late as 1968 it was stated that mid or late systolic clicks were not a feature of papillary dysfunction secondary to atherosclerotic heart disease.[6]

Abnormal left ventricular contraction has been increasingly recognized as an important component of the mitral regurgitation associated with papillary muscle dysfunction. In fact, several experimental studies have shown that

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Table III Patients with papillary muscle dysfunction secondary to coronary artery disease

Study	No pts.	ECG			Pan systolic murmur	Aneurysm
		Anterior	Inferior	Both	(%)	(%)
Cheng[9]	80	32	32	16	16	37 5
Shelburne et al[37]	14	—	—	—	36	44
Heikkila[19]	117	60	57	—	41	—

Accurate diagnosis is important because surgery can be life saving It was not until 1948 that the diagnosis was first made before death [11] The first successful operation for relief of mitral regurgitation following papillary rupture was not reported until 1965 [2] Surgery has been performed as early as the first two weeks after infarction [1]

Rupture of the posteromedial papillary muscle is several times more common than the anterolateral[12] because the latter has a more extensive collateral circulation [14]

Morrow and associates[29] described four patients with ruptured papillary muscles and severe mitral regurgitation necessitating valve replacement All four had holosystolic murmurs sinus rhythm and a fourth heart sound with severe congestive heart failure Three of the four had severe pulmonary hypertension from 60 to 80 mm Hg The average cardiac index was 1 8 L per minute per square meter [29]

The site of rupture primarily determines the clinical course Each papillary muscle provides chordae to both mitral leaflets The chordae arise from several apical heads which are extensions of the papillary muscle trunk [31,29] If the entire trunk ruptures then both leaflets are deprived of one half of their valve support and massive mitral regurgitation results with usually a rapid death If an apical head alone ruptures then the degree of mitral regurgitation is not as severe and the outcome is dependent upon the functional state of the infarcted ventricle [12,29,31]

The performance of left ventricular angiography after such a drastic event is crucial if ventricular function is reasonably preserved surgery may be life saving [12]

III Rupture of interventricular septum

Ventricular septal rupture occurs in 0 5 to 1 0 per cent of cases of acute myocardial infarction and 2 per cent of deaths from acute infarction will evidence it [16]

The septal perforation usually occurs any time from a few hours to two weeks after infarction and is seen in the first week in the majority of cases In 132 cases reviewed[35] it usually occurred in one to five days Selzer and group s[36] series of 10 cases averaged 2 6 days from the onset of infarction

The defect varies from a small tear to 3 cm in size in its widest dimension It always occurs in the muscular septum whereas 90 per cent of congenital septal defects are in the membranous septum [36] There is a common association with aneurysms of the septum and ventricular wall and approximately one half the patients will have an aneurysmal left ventricular bulge [7,36]

The magnitude of the shunt may vary from two to five times the systemic output, and moderate pulmonary hypertension (right ventricular systolic pressure of 60 to 80 mm Hg) is usually present [7,36]

The ECG may show conduction defects mostly right bundle branch block This was reported to occur in 39 per cent of cases in one report [35] It was also found that 75 per cent of cases were associated with an anteriorly located infarction [35] These differential parameters have been disputed, however by other authors [33,36]

The prognosis is grave in Sanders and colleagues [35] cases 54 per cent survived less than one week and only 13 per cent lived more than two months when treated medically Lee and associates[25] reported 220 patients of whom only 11 per cent lived beyond two months Oyamada and Queen[30] found only that seven per cent of 200 medically treated patients lived more than a year However prolonged survival has occasionally been noted the longest being 13 years [23]

Such a serious outcome under medical man

Table I Factors affecting the character of the murmur of papillary muscle dysfunction[6 9 12,37]

1 Degree of fibrotic contraction of the papillary muscle
2 Left ventricular contractility
3 Presence of left ventricular dyskinesia aneurysm
4 Presence of left ventricular dilatation

Table II Patients with myocardial infarction[19]

ECG infarction site	No of patients	Murmur of mitral regurgitation	
		No	%
Anterior	111	60	54
Posterior	76	57	75

isolated lesions of the papillary muscle do not cause mitral regurgitation unless there is accompanying left ventricular wall dyskinesia In these studies either formalin injections[40] were made into the base of the papillary muscle or constricting sutures were placed at the base of the muscle and resulted in isolated papillary muscle dysfunction[27] It was suggested that the papillary muscle per se played only a small role in closing the mitral valve in the presence of a normal left ventricle Shelburne and associates[37] found abnormal left ventricular contraction in 13 out of 14 patients with papillary muscle dysfunction and mitral regurgitation, and six had frank ventricular aneurysms They concluded that ventricular asynergy was as much at fault in the etiology of the mitral regurgitation as was the papillary disease They felt that the character of the murmur was dependent on the paradoxic motion of the area of dyskinesis if it were at the base of the papillary muscle Cheng[9] also stated that a ventricular aneurysm was a frequent (30 per cent) finding in papillary muscle dysfunction and that its role in the causation of the mitral regurgitation and congestive heart failure must be strongly considered. Thus the papillary muscle and its adjacent left ventricular wall function as an integral unit

The electrocardiographic (ECG) pattern of papillary dysfunction was thought to be characteristic as originally described by Burch and DePasquale[5] However no distinguishing ECG features have been consistently seen by subsequent investigators[21,37]

The location of the infarction in papillary muscle dysfunction is best related in terms of the anatomy of the blood supply The anterior papillary muscle is more abundantly supplied than the posterior and is less likely to be compromised during ischemia[14] The anterior papillary muscle receives branches of the left anterior descending and the left circumflex arteries The posterior muscle derives its supply from branches of the right coronary artery and left circumflex in 70 per cent from the right coronary alone in 20 per cent, and the left circumflex solely in 10 per cent of cases[9] However, several series reveal that there is an over all equal incidence of anterior and posterior papillary muscle dysfunction[9 19] This may be explained by the fact that anterior wall infarction is more common than posterior (Table II)

The course of papillary muscle dysfunction is quite variable Rapid onset of congestive heart failure may occur from the mitral regurgitation or there may be an insidious progression of heart failure over several years or it may remain only an incidental and even transient finding The competence of the left ventricle probably determines the outcome rather than the impairment to the papillary muscle[12]

Surgery may be necessary in severe mitral regurgitation with congestive heart failure unresponsive to medical management even though the papillary muscle may not have actually ruptured However, the anatomy of the underlying coronary disease and its amenability to revascularization, the contractile state of the left ventricle, and the presence of a ventricular aneurysm must be considered before a decision for valve replacement and possible saphenous vein bypass is made[9 12 37] Table III summarizes some features of papillary dysfunction

II Papillary muscle rupture

Rupture of the papillary muscle occurs in 0 9 per cent of acute myocardial infarctions[8 16 29] It presents as rapid onset left ventricular failure and pulmonary edema Death often occurs in the first 24 hours—18 per cent in less than one hour—and 80 per cent die in two weeks[34] Several prolonged survivals have been reported the longest being almost 14 years[4]

Papillary muscle dysfunction is usually a more benign lesion than papillary rupture and pulmonary edema is rare See Table IV for other features that may be of assistance in distinguishing the two entities

The murmur of mitral regurgitation secondary to left ventricular dilatation is in reality a form of spatial papillary muscle dysfunction The papillary muscles move laterally with ventricular dilatation and exert tension at an abnormal angle preventing coaptation of the leaflets This would be expected to resolve with ventricular compensation as the papillary muscle complex regains its proper mechanical leverage [6,12]

In summary if there is acute pulmonary congestion in a postinfarction patient with a systolic murmur the clinical distinction can be very difficult Cardiac catheterization and angiography may be necessary to determine the exact lesion status of ventricular function and the possibility of valve replacement septal repair aneurysmectomy or saphenous vein bypass procedure

V Case histories

Case 1 M W a 66 year-old white male insurance salesman, was in good health until the sudden onset of chest pain in January 1972 he was hospitalized in Rapid City S D with an anterior myocardial infarction He had ventricular tachycardia and cardiac arrest from which he was resuscitated. Between the first and second weeks of hospitalization he developed congestive heart failure responding to digitalis and diuretics He was discharged after one month but was readmitted two and six weeks later for symptoms of congestive failure including dyspnea on exertion and some paroxysmal nocturnal dyspnea He was referred to Colorado General Hospital for evaluation in May 1972 there fluoroscopy revealed an area of paradoxic dyskinesia in the anterior and superior lateral wall of the left ventricle. There was persistent ST elevation anteriorly and a ventricular aneurysm was diagnosed No murmur was heard. There was an S_3 gallop Because he was making gradual albeit slow improvement in his exercise tolerance further studies were deferred. In June he was again hospitalized with mild edema dyspnea and upper abdominal discomfort. For the first time a murmur was noted exactly five months after his infarction. In July 1972 he was again referred to Colorado General Hospital

Physical examination revealed a weak lethargic man the blood pressure was 105/70 mm. Hg the pulse was 92 and regular No cyanosis was seen the neck veins were distended at 90 to the angle of the jaw There were bilateral rales a thrill was felt at the left sternal border The first heart sound was decreased. The second sound did not close completely with expiration and third and fourth sounds were evident A Grade 3/6 holosystolic murmur was heard at the lower left sternal border it radiated to the axilla and less so to the base The liver was felt four fingerbreadths below the costal margin.

Table IV Differentiation of papillary muscle lesions[9]

Feature	Papillary dysfunction	Papillary rupture
S_1	Increased	Soft
ECG	Equal incidence of anterior inferior infarcts	Inferior twice as often[34]
Course	Pulmonary edema rare	Rapid profound pulmonary edema

The ECG showed an anterolateral infarction with persistent ST elevation, left axis deviation, anterior fascicular block with *intramural block, and left atrial enlargement.* There was cardiomegaly and pulmonary congestion on the chest roentgenogram.

It was felt by the house staff and cardiology consultants that this was most likely the murmur of mitral regurgitation.

Cardiac catheterization was performed on July 14 1972 and it showed a 4 4 to 1 left to right shunt Pressure in the right ventricle was 75/0 to 24 mm in the left ventricle it was 110/0 to 29 the angiogram demonstrated an aneurysm of the anterior wall of the left ventricle with moderate mitral regurgitation. On July 15 1972 an aneurysmectomy and repair of ventricular septal defect were done Postoperatively he had mental confusion and paranoid ideation for several weeks which slowly resolved. He was discharged on Aug 9 1972 with no evidence of congestive failure

Case 2 M M a 60 year-old white man in good health, with no prior cardiac history had chest pain and was hospitalized on June 1 1972 with an acute inferior wall infarction with acute enzyme and ECG changes A systolic murmur was first heard on the sixth day Symptoms of left sided failure were noted on the twelfth day and he was transferred to the Denver Veterans Administration Hospital on the fifteenth day because of congestive failure not responsive to digitalis and diuretics

Physical examination on admission there revealed that the blood pressure was 105/70 mm. Hg the pulse was 125 and regular There was no venous distention A few basilar râles were noted and a Grade 3/6 holosystolic murmur was heard at the lower left sternal border which radiated to the apex but not to the axilla An S_3 gallop was heard and there was no edema

The ECG demonstrated an inferior infarction Normal heart size and pulmonary edema were seen on the chest roentgenogram

On the seventeenth day after onset severe pulmonary edema occurred he was taken to surgery on the eighteenth day where a ruptured papillary muscle of the anterior leaflet with a completely necrosed base of the papillary muscle was found The chordae and papillary muscle remnant were prolapsed into the left atrium A medium sized Beall disc type valve was inserted. There were no symptoms of congestive failure postoperatively but he developed an empyema which eventuated in a prolonged hospitalization with drainage and antibiotic treatment

Case 3 J C a 63 year old white man was in good health until the onset of interscapular and anterior chest pain in February 1973 He was admitted to a South Dakota hospital

agement has led to a surgical approach to this problem The first reported surgical repair of a perforated interventricular septum after myocardial infarction was in 1957 A 49 year old man, 11 weeks after acute inferior infarction, had a successful repair of the defect but died 45 days later [10] Many surgical successes have been recorded since then A recent review of 42 cases with surgical intervention reported as of December 1970, stated that the surgical death rate in the hospital was 31 per cent[17] (vs 67 to 89 per cent medical death rate at two months in three series of 91, 157, and 220 cases) [33,25,30] A ventricular aneurysm was found in 55 per cent of the patients and aneurysmectomy at the time of septal repair was thought to favorably affect survival [17]

Selzer and associates[36] have stated that surgery may not always be necessary as the shunt may be well tolerated and suggested that the indications for surgery were (1) emergency operation for shock or congestive heart failure unresponsive to treatment and (2) elective closure for those with persisting heart failure Although successful surgery has been done as early as twelve days after infarction,[3] it is felt that a delay of eight weeks is best because this allows enough collagen invasion to hold the sutures in the septum [37] However, in a deteriorating situation, earlier surgery may be necessary DeWeese and co workers[13] reported operations on five patients from nineteen to forty two days after infarction all of whom did well following surgery

IV Differential diagnosis

The ECG is of little help in an individual case, and as previously mentioned the pattern that Burch and DePasquale[5] felt to be characteristic of papillary muscle dysfunction is not reliable in distinguishing septal rupture from papillary rupture [36]

The chest film likewise offers no dependable assistance as pulmonary hypertension and congestion will obscure the interpretation of pulmonary blood flow patterns Acute mitral regurgitation characteristically has a normal sized left atrium [12]

Many sources state that the distinction between papillary muscle rupture or dysfunction and rupture of the interventricular septum can be confidently made on physical examination

The characteristic features of papillary muscle rupture are said to be a loud apical low pitched holosystolic murmur radiating to the axilla, usually not accompanied by a thrill associated with an inferior infarction prominent left ventricular failure, and usually no intraventricular conduction defects [16,18,35] Although some overlap is admitted in the distinction, it is claimed that usually there are enough distinguishing features to make the diagnosis [18]

On the other hand, septal rupture is said to present as a murmur along the left sternal border without radiation to the axilla, a thrill in 50 per cent of cases, association with anterior infarction, and frequent conduction disturbances [16,18,35]

However, the specificity of these features has been questioned.[33,36] In Selzer's 10 cases, the murmur of septal perforation was apical or equally as loud at the apex as at the left sternal border and radiated to the axilla in one half of the patients. Only three had a thrill eight had an inferior not anterior infarction Only one of 10 had a conduction defect and that preceded the infarction

Several factors may alter the character of the murmur of septal rupture A large defect can produce systemic right ventricular pressure which will change the murmur's features. If enough left ventricular dilatation is precipitated and mitral regurgitation ensues, the murmurs may overlap to obscure recognition of classic septal rupture

Ultrasound may be of value in demonstrating a prolapse of the mitral leaflet into the left atrium in papillary muscle disease [22]

Only two cases have been reported of simultaneous papillary muscle involvement and perforated interventricular septum after myocardial infarction [32,38]

Cardiac catheterization is required to be certain of the diagnosis and should be undertaken as an emergency measure if there is rapid deterioration, in an appropriate setting [33,36] Severely ill patients may not be able to tolerate angiography and, in these instances bedside catheterization of the right heart with a Swan Ganz catheter will allow the diagnosis of a ruptured septum by demonstrating an oxygen stepup greater than one volume per cent between the right atrium and right ventricle Giant v waves in a pulmonary wedge tracing may suggest acute mitral regurgitation as the diagnosis However the angiographic technique offers a more complete preoperative evaluation if the patient can tolerate it [26]

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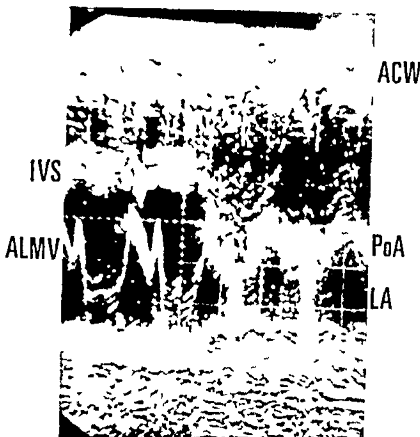


Fig 1 Echocardiogram of M L demonstrating numerous echoes in systole as seen in prolapse of the anterior mitral valve leaflet Also there is excessive posterior excursion of the leaflet into the left atrium *ACW* = anterior chest wall *IVS* = ventricular septum *PoA* = posterior aortic wall *LA* = left atrium *ALMV* = anterior leaflet mitral valve

where ECG showed an acute inferior wall infarction. On the third day a loud systolic murmur was noted and evidence of congestive heart failure appeared He was digitalized and given diuretics

After three weeks he was transferred to Colorado General Hospital because of unresponsive congestive heart failure At physical examination on admission the blood pressure was 110/60 mm Hg the pulse was 100 and he was markedly dyspneic while sitting There were elevation of the venous pulse to the angle of the jaw at 90 bilateral basilar râles 4+ ankle edema and tender hepatomegaly 6 cm below the right costal margin The first heart sound was decreased a loud S_3 was heard and there was a Grade 3/6 holosystolic murmur at the apex which was radiated toward the axilla but was also well heard toward the left sternal border No thrill was ap preciated

The ECG demonstrated an inferior wall transmural infarc tion with left atrial enlargement and probable left anterior fascicular block Cardiomegaly and pulmonary congestion were seen on portable chest film

The impression was acute mitral regurgitation although it was felt that a ventricular septal defect was possible. A right heart catheterization on Feb 24 1973 revealed an oxygen stepup of 63 to 82 per cent from the right atrium to the pulmon ary artery pulmonary artery pressure of 80/50 a mean wedge of 18 mm and a V wave of 28 compatible with a ventricular septal rupture and mild mitral regurgitation Emergency sur gery was performed that day and a quarter sized defect was found in the mid muscular septum with friable edges. One week after surgery there was no audible murmur but he re mained in moderate congestive heart failure.

Case 4 L. M a 56 year-old white woman was in excellent health with no prior cardiac history until Aug 14 1972 when she had the sudden onset of crushing chest pain of 2 hours duration She was hospitalized at Swedish Medical Center coronary care unit and 24 hours later a loud systolic murmur was first heard Slight enzyme elevation occurred and ECG showed ST T wave depression inferiorly She re mained in the unit for eight days with no evidence of heart failure or arrhythmia and was transferred to Colorado General Hospital on Aug 22 1972

Physical examination showed a thin woman in no distress with a blood pressure of 120/80 mm. Hg and a pulse of 80 and regular There was no cardiomegaly or jugular venous disten tion The lungs were clear and there was no edema. Faint third and fourth heart sounds were heard. The first heart sound was loud with a very early systolic click appreciated The click slightly increased with inspiration A Grade 3/6 holosystolic murmur was heard equally well at the left ster nal border and the apex and there was slight transmission to the base and the axilla

The ECG did not reveal a transmural infarction but only nonspecific inferior wall ST T changes The chest roentgenogram was normal as were serum enzymes

She experienced occasional chest pain during her hospi talization but at no time was there any evidence of heart failure An ultrasound examination on Aug 25 suggested prolapse of the anterior leaflet of the mitral valve (see Fig 1) She was discharged on Sept 2 1972 on nitroglycerin for further follow up in the cardiology clinic

ability of indirect techniques to measure arterial flow precisely in man or to species differences in the visceral vascular responses to exercise

In comparing the mechanisms responsible for augmenting oxygen delivery to cardiac versus skeletal muscle two important differences exist[8, 13] First the myocardium depends almost entirely upon increases in coronary arterial blood flow for oxygen extraction is nearly complete even at rest, with coronary sinus blood containing only 2 to 5 volumes per cent of oxygen That is the myocardium is a flow dependent tissue Skeletal muscle on the other hand, is capable of a threefold increase in oxygen extraction above resting values Second, skeletal muscle is able to continue contracting in the absence of oxygen, whereas cardiac muscle which is almost strictly aerobic does not have this ability and ceases to contract when it has incurred only one fifth of the oxygen debt that skeletal muscle can develop[1] Coronary blood flow is largely diastolic During exercise a fall in coronary vascular resistance accounts for the observed increase in coronary blood flow despite a decrease in diastolic time per minute[18] Coronary perfusion pressure (aortic diastolic pressure) remains virtually constant The fall in coronary resistance may be mediated by an increase in myocardial release of adenosine a potent coronary vasodilator in response to hypoxia or to an increase in oxygen consumption per se[19]

The major factors determining myocardial oxygen consumption (MVO_2)are left ventricular wall tension time and contractility[20,21] During exercise tension time per minute rises because of increments in heart rate and systolic blood pressure Changes in left ventricular volume should also occur during upright exercise but little information is available in this regard Contractility is increased by catecholamine release and by the increased heart rate itself An increase in fiber shortening work may also play an important role in determining MVO_2 during exercise[22]

Clearly a number of adaptive mechanisms exist by which the increased oxygen demands of exercise can be met The age sex, and physical conditioning of the subject affect these mechanisms thus influencing exercise capacity[8,10,23] Above age thirty heart rate cardiac output, oxygen consumption and stroke volume during maximal exercise all decrease progressively Women compared to men have smaller hearts and blood volumes lower hemoglobin concentrations and generally are not as well conditioned. Consequently average maximal cardiac output, oxygen consumption and exercise capacity are lower for women than for men When physical conditioning is improved, enhanced delivery of oxygen to exercising muscles occurs. This change is mediated by increases in stroke volume and cardiac output probably due in turn to an augmentation of hemoglobin and blood volume A more efficient distribution of cardiac output to exercising muscles and changes in autonomic tone may also occur with physical training

The type of exercise performed is another important consideration when evaluating a subject s response to stress testing The circulatory response to exertion will depend on whether the exercise is conducted in the upright or supine position[8,24,25] whether it is dynamic or isometric[26,27] whether it is performed with the upper or lower extremities[6,25] and whether it is executed on a bicycle ergometer steps, or treadmill.[25,28]

At rest, heart rate is higher while stroke volume and cardiac output are lower in the upright as opposed to the supine position This response is due to a decrease in venous return during upright posture The same differences exist during mild to moderate exertion however with strenuous exertion venous return and stroke volume become equal in the two positions Higher maximal cardiac outputs and higher maximal oxygen consumptions may be attained in the upright position Whether this is due to noncardiovascular effects of strenuous exercise in the supine position or to cardiovascular limitations in this position is uncertain

The use of isometric or static exercise in stress testing has become increasingly popular because of its convenience Sustained muscular contraction produces a marked pressure load on the heart by evoking large increments in blood pressure with relatively less augmentation of heart rate and cardiac output With less strenuous isometric effort 20 to 30 per cent maximal voluntary contraction stroke volume and systemic resistance show little change The execution of 50 per cent maximal voluntary contraction often causes a decrease in stroke volume and increase in systemic resistance At contractions below 15 per cent maximal voluntary con

The exercise test as a diagnostic and therapeutic aid

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The growing emphasis on early diagnosis and prevention in cardiovascular disease has made the exercise laboratory an integral part of clinical cardiology Although evaluation of cardiovascular function in the resting state provides much useful information examination of the circulatory response to stress can be much more sensitive and informative [1] Since exercise is the most physiologic, familiar, and convenient form of stress exercise stress testing has received much recent attention as a diagnostic therapeutic, and investigative aid.

In considering applications of exercise testing to cardiovascular disease familiarity with normal physiologic responses to exercise the design of exercise protocols and the many noncardiac factors which can affect the circulatory response to exercise is essential

Exercise physiology

The initiation of exercise† provokes a complex interaction of humoral metabolic, neurologic and hemodynamic responses [2-10] This discussion will concentrate on hemodynamics Exercise capacity is normally determined by the availability of oxygen for the metabolic requirements of cardiac and working skeletal muscle

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†Unless specifically noted, exercise will refer to upright dynamic exercise

Augmentation and redistribution of cardiac output (CO), as well as increased tissue extraction of oxygen from blood are important mechanisms for increasing oxygen transport and delivery during exercise Although oxygen delivery is improved by a rise in hemoglobin concentration during strenuous exercise,[8] neither oxygen diffusion in the lung nor the oxygen carrying capacity of red blood cells is a critical factor affecting exercise performance in normal man [11]

Cardiac output increases during exercise in a linear relation to total body oxygen consumption until the subject exceeds 40 per cent maximal oxygen consumption at which point the relation becomes curvilinear [12,13] This augmentation in cardiac output is accomplished by increases in heart rate myocardial contractility [9] and stroke volume [8, 9, 14] and is associated with a rise in central blood pressure and a fall in peripheral vascular resistance [15]

The decrease in total peripheral vascular resistance results from marked *local* vasodilation in *exercising muscles* a response which overcomes the opposing effects of a generalized increase in activity of sympathetic noradrenergic fibers to both resistance and capacitance vessels [8] Some difference of opinion exists regarding changes in regional blood flow during exercise It is agreed that blood flow to cardiac and active skeletal muscle increases while vasoconstriction occurs in inactive muscle and in the visceral vascular beds It had been concluded that this vasoconstriction resulted in a *redistribution* of blood flow away from the visceral beds in favor of exercising muscle [10] However recent studies suggest that visceral blood flow does *not* decrease despite the increase in visceral vascular resistance [16] This discrepancy may be due to the in

imal stress or a symptomatic endpoint be used and that the amount of stress required be quantifiable and reproducible in itself and in its relation to MVO_2.

Exercise testing as a diagnostic aid has relied almost exclusively on electrocardiographic indicators of ischemia. Electrocardiographic changes following exercise induced angina were described in 1928 by Feil and Siegel[37] and more extensively characterized shortly thereafter by Wood, Wolferth and Livesy.[38] However, wide spread interest was not evoked until Master and Jaffee[39] incorporated electrocardiographic observations into their two step stress test.

The Master test is a single load stress test in which the subject performs a preselected number of trips up and down two nine inch steps in a prescribed time period, with recording of Leads II and $V_{3 \text{ through } 5}$ intervals *after* exercise. The original 90 second test has been extended to 3 minutes (the double Master's) and the number of trips further increased by 15 per cent (the augmented double Master's). While a variety of changes in the electrocardiogram have been proposed as indicators of ischemia, only the occurrence of a *flat* ST depression of at least 0.05 millivolt in magnitude has been widely accepted and validated for the Master's test. Flat ST depression does not necessarily connote ischemia in patients with left ventricular hypertrophy or in those patients receiving digitalis.[40-42] While the safety and diagnostic significance of exercise testing in patients with resting electrocardiographic abnormalities have been questioned in the past, recent evidence suggests that such abnormalities do not render the test less valid or unsafe.[43]

Assessment of the specificity and sensitivity of the Master's test, as well as other electrocardiographic stress tests, has proved a vexing problem. Early claims of extreme diagnostic accuracy were contested on the basis of carefully correlated clinical observations.[44] Recently, coronary angiography has been a powerful tool in assessing the value of electrocardiographic stress testing. However, there remains a fundamental difference in kind between the anatomic information about the large coronary arteries conveyed by the arteriogram and the pathophysiologic answer sought with electrocardiographic stress testing.[45] Thus *all* patients with occlusive large vessel coronary artery disease may not have stress induced ischemia. Similarly, *all* patients with stress induced ischemia may not have occlusive large vessel coronary disease.

A solution to the problem inherent in comparing anatomic with physiologic information would require an independent objective means of recognizing myocardial ischemia. A variety of approaches, including analysis of myocardial lactate metabolism, systolic time intervals, echocardiography, and radioisotopic myocardial perfusion scanning have been investigated, but no entirely satisfactory method is yet in hand.[46-49]

Studies correlating electrocardiographic responses to the Master's test with coronary angiography suggest that the test has a *sensitivity* (per cent of true positives detected) of 48 to 66 per cent and a *specificity* (per cent of true negatives rejected) of 80 to 83 per cent in detecting obstructive coronary atherosclerosis.[50-53] Factors which contribute to the limited sensitivity and specificity of electrocardiographic stress testing have been extensively explored. An important limitation of the Master's test is that in some patients the single work load used requires an increase in MVO_2 inadequate to elicit ischemic manifestations. Consequently, a variety of progressive multistage treadmill and bicycle ergometer tests have been introduced.[35] These tests may be submaximal or maximal in end point. Submaximal tests such as that proposed by Sheffield, Roitman, and Reeves[40] commonly strive to achieve 80 to 90 per cent of the average predicted maximum heart rate for individuals of a given sex and age, unless symptoms supervene. ST depression in excess of 0.1 mv is regarded as abnormal. Comparisons with coronary angiography suggest that upright submaximal tests commonly have a sensitivity of about 80 per cent and a specificity of about 90 per cent.[54,55] The normal range of maximal heart rate is fairly wide so that average values used in submaximal testing for some patients may be misleading. Truly maximal tests may have a higher electrocardiographic yield.[56] Available correlations with angiography, however, do not support this contention.[57-59]

Nevertheless, maximal testing does safely permit direct observation of exercise related symptoms, functional classification, and documentation of therapeutic responses. Thus we presently perform maximal testing whenever possible. Failure to record the electrocardiogram *during* exercise may result in failure to identify

traction steady state conditions are achieved, however, with more intense effort the circulatory responses continue to increase in magnitude until fatigue intervenes Similar hemodynamic responses are observed regardless of size or location of the muscle group employed. Compared to dynamic exertion, there is a disproportionate rise in CO relative to oxygen consumption

Arm exercise produces a greater increase in heart rate and blood pressure than leg exercise at the same oxygen consumption, but the increases in cardiac output and stroke volume are less In addition lower maximal cardiac output and oxygen consumption are usually achieved during arm exertion The explanation for these differences has been ascribed to a lesser fall in systemic resistance during arm exercise because of the smaller muscle mass involved We must emphasize, however that combined leg and arm exercise does not result in higher maximal cardiac output and oxygen consumption than leg exercise alone This indicates that cardiac output and oxygen consumption are independent of exercising muscle mass once a certain ill defined critical mass is exceeded The limiting factor in this setting is the capacity of the heart to deliver oxygen to exercising muscles

As would be expected from consideration of exercising muscle mass only small differences in maximal cardiac output and oxygen consumption exist when bicycle treadmill and step exercise are compared Cycling elicits the lowest maximal levels and running on a treadmill elicits the highest Although the difference is statistically significant it is less than seven per cent Bicycle exercise may be inherently more stressful than treadmill exertion since the former evokes higher heart rates and blood pressures at the same work load The mechanism responsible for this difference is not clear but it may be related to the discomfort associated with the bicycle seat

Exercise protocol

In addition to those factors already described the exercise protocol itself may have a marked effect on the circulatory response to exercise [29]

The interpretation of a stress test usually requires a comparison of the individual s response with either previously determined normal responses or with a previous test by the same subject Therefore the test protocol and results must be reproducible The major considerations necessary to insure reproducibility include (1) the patient should be familiar with the laboratory equipment, (2) a three to five minute warm up period prior to nongraded strenuous exercise should be utilized, (3) each grade of exercise should be sustained long enough to insure steady state conditions[30,31] (4) in the evaluation of therapeutic interventions in patients with angina pectoris, the starting level and exercise increments should be selected so that either angina or another preselected endpoint occurs between the fourth and seventh minute of exercise[29], (5) ample recovery time should be allowed between successive exercise periods[32], (6) a constant and comfortable room temperature should be maintained throughout the test, and this temperature should not vary from day to-day[8,33] (7) the subject should come to the exercise laboratory in the fasting state[8,34], and (8) an easily identifiable and reproducible endpoint should be designated.

An important overall consideration in selecting an exercise protocol is that the physician should not be committed to a single fixed system, but should adapt the stress test to the individual patient and the information desired. A number of exercise protocols have been developed which provide flexibility and yet meet these criteria The reader is referred to them for further details [24 35 36]

Now that we have examined the cardiovascular hemodynamic response to exercise in normal individuals and have considered some of the factors which can influence this response let us examine how exercise testing can provide us with useful information in the diagnosis and evaluation of cardiovascular disease

Ischemic heart disease

Exercise testing has been used to explore problems in the diagnosis therapeutics functional classification, and epidemiology of ischemic heart disease One physiologic strategem is common to all these applications the increase in MVO_2 produced by exercise is used to elicit manifestations of myocardial ischemia that are absent in the resting state However details of exercise protocol design as well as endpoint criteria vary considerably according to the purpose for which exercise testing is employed Studies of functional classification, pathophysiology and therapy of ischemic heart disease requre that max

reduction in MVO_2 for any given level of external work since triple product at angina remains the same [66] A similar phenomenon probably ac counts for the efficacy of propranolol [67] The prin cipal effect of physical training on exercise tolerance in patients with angina is a reduction in triple product at any level of external work [68] However physical training also appears to pro duce a small but significant, increase in triple product in angina.[68, 69] This could mean that per fusion of potentially ischemic myocardium is augmented, but failure of triple product during pacing induced angina to show parallel changes after training makes this less likely Since in direct indices such as triple product do not take into account a number of additional important determinants of MVO_2, such as ventricular size and contractility it is possible that changes pro duced by physical training may affect these other variables and account for the observed changes in triple product Exercise studies have also dem onstrated that the familiar decrease in exercise tolerance experienced when patients with angina are exposed to cold is related to an in crease in peripheral resistance and arterial pressure [33] which presumably increases MVO_2 for any level of external work In contrast postpran dial reductions in exercise capacity are related to increases in heart rate and, to a lesser degree blood pressure at any given level of exercise As in cold exposure the triple product at angina re mains constant, while the triple product at any given level of external work is increased in the postprandial state

The effects of supine dynamic and isometric exercise on LV function in coronary artery dis ease have been studied extensively [21 70 72] Abnor mal elevations of end diastolic pressure occur and may result from segmental impairment of LV compliance due to ischemia Concomitant im pairment in stroke work stroke volume systolic ejection rate and contractility have also been noted in response to exercise in this setting All of these changes may occur before after or in the absence of chest pain and ST changes

Maximal exercise testing lends itself to the evaluation of therapeutic interventions in pa tients with angina pectoris. Such studies have demonstrated the efficacy of physical training [68 69] successful coronary bypass surgery [73 74] propranolol [75 76] sublingual nitroglycerin [65 66] combinations of propranolol and sublingual nitroglycerin [77] and carotid sinus stimulation [79] in enhancing exercise capacity in patients with cor onary artery disease Because exercise tests can be repeated at frequent intervals they are also useful in determining the duration of action of anti anginal drugs Such studies have shown that sublingual isosorbide dinitrate and other pur ported long acting sublingual nitrates do not have a longer duration of action than sublingual nitroglycerin when comparable doses are used,[65 79] while nitroglycerin ointment clearly has long lasting anti anginal effects [80] Results with a variety of other purported long acting nitrates are less clear cut. This may in part reflect prob lems in exercise protocol design [26,81]

Exercise testing can also be used for the func tional classification of individual patients Such classification is of value as an adjunct to the clini cal history as an index in the supervision of physical training in the selection of patients for coronary surgery and possibly as a prognostic in dicator [82 84]

The prognostic value of exercise testing in asymptomatic individuals is substantial Doyle and Kinch[85] noted that the development of an ab normal exercise test under observation in an in dividual who was asymptomatic at the outset of their study was associated with an 85 per cent risk of clinical ischemic heart disease within 5 years. Individuals with persistently negative tests had a 1 5 per cent risk In 30 per cent of sub jects developing clinical ischemic heart disease an abnormal exercise test was the first abnor mality noted. In the above study an abnormal exercise test at intake of the study increased risk of overt ischemic heart disease but was less ominous than development of a new abnor mality The prognostic value of an abnormal stress in asymptomatic persons is confirmed by a number of other studies [86 90] The increase in risk reported by Bruce and McDonough[86] was as high as 13 fold However Blackburn Taylor and Keys[89] observed that when known risk factors were appropriately matched among United States citizens only a threefold increase in risk was noted. Moreover while risk increases were observed in six foreign populations these risks did not achieve statistical significance

Valvular heart disease

When applied to valvular heart disease exer cise testing is of limited diagnostic value but is

abnormal responses that promptly disappear at rest In one published series, 11 per cent of abnormal responses were noted only during exercise [53] Accordingly, monitoring during exercise has become an integral part of exercise testing in order to increase diagnostic accuracy as well as safety

The influence of electrocardiographic lead selection has been explored by Blackburn [60] Conventional Leads II, aV_F and V_3 to V_6 contain as much ST segment information as the full 12 lead tracing [60] Lead V_5 alone detects nearly 90 per cent of exercise induced ST segment changes while ST segment changes limited to inferior or vertical leads are relatively uncommon Finally a bipolar lead with the positive electrode at the V_5 position and the negative electrode at the manubrium (CM_5 lead) appears to be as sensitive as the 12 lead electrocardiogram and more sensitive than the Frank XYZ leads in detecting exercise induced ST segment changes [60]

The quantitative relationship between the magnitude of ST segment displacement and angiographic findings has been examined in several series [50 51 54] In brief, the larger the ST segment change required for an abnormal result, the more specific and less sensitive the test For the Master s test, a 0 05 mv ST segment change offers the best combination of sensitivity and specificity, while for multistage submaximal and maximal tests 0 1 mv is the most satisfactory criterion The presumption that ST segment displacement must be flat to be significant has also been re examined using computer quantitation and angiographic correlation [61] The data obtained indicate that a slope of 1 mv per second or less is abnormal during and immediately after exercise when 0 1 mv ST depression is present

Even if we combine *maximal* testing with optimal electrocardiographic monitoring and optimal interpretative criteria it appears unlikely that the sensitivity of exercise electrocardiography can exceed 80 to 85 per cent or specificity exceed 95 per cent when judged by angiographic correlation Accordingly, efforts have been made to use other noninvasive parameters together with stress testing for the detection of coronary artery disease Differences in systolic time interval responses to exercise exist between patients with coronary disease and normal control subjects [47] However, the overlap is sufficiently great to make the diagnostic usefulness of systolic time intervals uncertain An initial report suggests that the echocardiogram in patients with angina pectoris demonstrates absence of the normal increase in posterior wall diastolic relaxation slope during exercise and that this slope actually decreases after the onset of angina [49] The potential usefulness of this observation for diagnostic stress testing remains to be explored. Finally myocardial perfusion scanning may prove to be a useful means of identifying exercise induced perfusion defects [49]

When maximal exercise testing is performed, angina is commonly elicited in patients with obstructive coronary artery disease even though some patients of this type show no diagnostic ST segment changes Thus, the production of chest pain itself is of potential diagnostic value Several recent studies have pointed out that exercise induced pain is at least as specific as ST segment changes in the recognition of obstructive coronary atherosclerosis while the combination of pain and ST change is entirely specific, albeit less sensitive than either parameter alone [58,59] In our laboratory, we presently report as abnormal exercise tests in which despite the absence of ST changes, persistent chest pain begins during exercise and disappears within minutes after cessation of exercise It may also be helpful as recommended for functional evaluation by Kattus [62] to allow the patient to exercise until chest pain is moderately severe This procedure is safe and may increase the yield of ST segment abnormalities since some patients develop ST segment changes only after the onset of angina

Pathophysiologic studies of the effects of exercise on patients with coronary artery disease have centered on two issues hemodynamic determinants of the onset of ischemia and the effects of ischemia on left ventricular function Heart rate left ventricular wall tension and the duration of systole are major determinants of MVO_2 [20 21] Indices derived from these variables such as the rate pressure product or the 'triple product (rate times systolic blood pressure times left ventricular ejection time) have shown a reproducible relationship to MVO_2 and to onset of ischemic pain in a given individual when the conditions of stress are held constant [29 60 63-65] After sublingual administration of nitroglycerin enhancement of exercise tolerance in patients with angina is probably largely attributable to

most helpful in identifying cardiovascular dys function and in the detection of its progression. During both upright and supine exercise, a number of hemodynamic parameters and indices have been measured and calculated in patients and compared with values obtained in normal subjects These parameters include total body oxygen consumption, intracardiac pressures, cardiac output at varying intensities of exercise[91, 92] and exercise capacity[93]

Upright exercise tests[92, 93] offer certain advantages over supine studies since they are more easily performed and more nearly resemble the type of stress the cardiovascular system is exposed to during normal activity The demonstration that the more intense the stress, the better the separation between normal and impaired circulatory responses,[1, 92] provides still another reason for performing upright exercise tests, since strenuous exercise cannot easily be carried out in the supine position

As we have discussed in the introduction a number of noncardiac factors influence the results of an exercise test and make its interpretation difficult. In addition to those elements already listed poor motivation and/or malingering can adversely affect exercise performance An experienced examiner can usually adjust for these factors, but occasionally the examiner is left with an inexplicable or borderline result and is unable to determine whether or not cardiovascular dysfunction is present. Various hemodynamic indices have been developed to help make this distinction[1, 94] None however appears to be as sensitive and specific as the circulatory index developed by Epstein and associates[1] According to their method each subject is studied at rest, during mild exercise, and during intense exercise By interpolation the cardiac index is determined at a pulmonary arterial saturation of 30 per cent and compared with values obtained in normal subjects If the most intense exercise the patient can perform does not produce a pulmonary arterial oxygen saturation of 30 per cent or less it is likely that exercise capacity is limited by noncardiac factors Using this technique, one is able to overcome such factors as poor motivation, malingering, and poor physical condition, and to identify those subjects with an impaired circulatory response to exercise Although this test requires a right heart catheterization, we have found it to be particularly helpful when any doubt exists as to whether an individual has a normal or impaired circulatory response to exercise

Although cardiovascular dysfunction can usually be identified and its progression detected using Epstein s method, quantification of the dysfunction by the use of more easily performed stress tests has not proved as successful. Two of the studies cited previously[92, 93] have employed the measurement of total body oxygen consumption and heart rate during graduated exercise testing in order to separate patients into groups corresponding to the New York Heart Association functional classification[95] It should be noted, however that the separations are not clear, and there is significant overlap among the different groups. Denolin, Messin and Degre[93] used an extrapolation to determine the physical working capacity of an individual at a heart rate of 170 (PWC 170) Although the validity of such an extrapolation has been demonstrated in normal subjects and in patients without congestive heart failure its application to patients with congestive heart failure is uncertain In view of the finding that patients with congestive heart failure have an impaired heart rate response to excercise[96] it would seem advisable to avoid this form of extrapolation in this group Failure to take this fact into account may be the cause of the significant overlap in Denolin s groups. Patterson and associates[92] utilized total body oxygen consumption at maximal exercise to separate their patients into functional classes The overlap present in their study may be due to the noncardiac considerations we have discussed, a possibility that could be examined by applying Epstein s test to those patients whose exercise response did not correspond to their clinical classification Furthermore, the clinical classification system that these and most other studies use as their standard of comparison for the exercise tests may be less sensitive and less specific than the stress test itself Long term follow up and repeated evaluations should answer this question

The absence of longitudinal studies correlating the findings of stress testing with long term clinical follow up of patients with valvular heart disease is striking The need for such investigations to evaluate the sensitivity of the various tests and the therapeutic significance of the information so obtained cannot be overemphasized

Data are available on repeated stress testing before and after a number of acute medical[97-99] and surgical[100-102] therapeutic interventions Through the use of strenuous upright exercise important information was obtained concerning the value of digoxin in valvular heart disease[97 99] diuresis in congestive heart failure[98] and weight reduction in mitral stenosis[99] The studies before and after valve replacement[101 102] did not show clear cut improvement, but these studies utilized mild to moderate supine exercise and thus may have not been sufficiently sensitive Moreover a more significant finding may be the lack of progressive deterioration of cardiovascular function We feel that the use of stress testing before and after therapeutic interventions and during long term clinical follow up will permit a more rational therapeutic approach to patients with valvular heart disease

At the bedside and in the catheterization laboratory where dynamic exercise is often impractical isometric exercise has received increasing use At the bedside handgrip isometric stress has been employed in the sometimes difficult differentiation between the murmur of mitral regurgitation and apical radiation of the murmur of aortic stenosis since it enhances the former but not the latter However the use of handgrip may be more important in the detection of abnormalities of left ventricular function in patients during cardiac catheterization[27 72]

Krayenbuehl and co workers[72] used isometric handgrip exercise to detect abnormal V_{max} responses which were not apparent in measurements made before stress As the authors correctly state the prognostic significance of these findings is uncertain and as with dynamic exertion long term follow up is a necessity

Congenital heart disease (CHD)

As in valvular heart disease exercise testing in patients with congenital heart disease is most useful in detecting cardiovascular dysfunction and in evaluating therapeutic interventions The same theoretical and practical considerations regarding the form and intensity of exertion and the exercise protocol discussed in the previous section are relevant. A recent report by Epstein and co workers[103] describes the presence of impairment of cardiac function in patients after operative repair of atrial septal defect or tetralogy of Fallot despite a lack of symptoms and despite normal or near normal hemodynamics at rest and absence of arrhythmias residual shunts or pulmonary hypertension Using intense upright exercise these investigators detected abnormalities in the cardiac output response to exercise in both groups and demonstrated the development of sizable gradients across the right ventricular outflow tract in patients with totally corrected tetralogy of Fallot. Nevertheless the circulatory response to exertion and exercise capacity were remarkably good after repair of Fallot s tetralogy especially in light of the complexity of the anatomic deformity and the extent of the operative repair The long term significance of the abnormalities identified in the above study remain to be determined. In patients with congenital heart disease responses to upright exercise are particularly useful in explaining apparent discrepancies between clinical symptoms and physical signs or resting hemodynamics Exercise can also be helpful in assessing the value of various forms of medical therapy such as inotropic agents diuretics and phlebotomies and in making decisions regarding operative intervention

Sequential studies employing dynamic or isometric exercise testing should permit the cardiologist to develop more reliable therapeutic guidelines The application of this principle may be reflected in the finding that after surgical closure of ventricular septal defects the degree of impairment of circulatory response to exercise may be related to age of the patient at the time of operation[100] Thus the need for longitudinal exercise studies of patients with cardiovascular abnormalities again must be emphasized. Although it may be helpful to identify abnormal responses to exercise at a specific time in a patient s course we still are uncertain as to the long term significance of such information In order to learn more about the natural history of the various forms of CHD long term follow up of patients with exercise testing is needed.[105]

Arrhythmias

Ventricular premature beats (VPB s) are common during and immediately after exercise testing Atrial premature beats are somewhat less commonly provoked. Sporadic VPB s per se do not connote heart disease but are more common in patients with clinically suspected disease especially coronary artery disease[106 107] More

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over, complex and sustained ventricular arrhythmias are largely limited to patients with heart disease Among patients with coronary disease, VPB s are associated with more severe disease [108] The prognostic significance of exercise induced arrhythmias in ischemic heart disease is uncertain but clearly warrants further study It has been suggested that, in high risk populations, physical conditioning reduces the frequency of VPB's induced by exercise [109] Suppression of resting VPB's by exercise induced tachycardia does not imply that the underlying process is benign and is common in patients with severe coronary artery disease [107] VPB s occur more commonly in the recovery period than during exercise itself

A 75 per cent prevalence of exercise induced arrhythmias including complex ventricular arrhythmias has been described in one study of the click systolic murmur syndrome,[110] but a similar study found only an 11 per cent prevalence with advanced arrhythmias in less than 1 per cent [111] Differences in the study populations may account for these discrepancies The prognosis of exercise associated arrhythmias in this context has not yet been established.

Arrhythmias produced by exercise are often asymptomatic and of uncertain prognostic significance When the rhythm disturbances are either symptomatic or alarming per se (ventricular tachycardia R on T PVC s, and multiform PVC s) the efficacy of therapy can be judged by serial exercise testing Development of frequent multiform VPB s or two or more ventricular beats in a row during exercise is a reasonable indication for cessation of the stress test although only three or more consecutive ventricular beats have been regarded by some as an indication for desisting [112]

The appearance or worsening of arrhythmias with exercise in patients receiving digitalis preparations may be an early indication of digitalis excess [113] Although the significance of this response is not certain, it may be prudent to withhold the drug until exercise induced arrhythmias disappear Further investigation is necessary in order to define the true significance of such arrhythmias

Hemodynamic measurements during exercise in patients with atrial fibrillation before and after cardioversion to normal sinus rhythm have demonstrated improved hemodynamic responses during sinus rhythm [114] Similar measurements in individual patients would be helpful in determining how much effort should be directed toward repeated cardioversions and suppressive therapy

While exercise electrocardiography is clearly a useful adjunct in the assessment of arrhythmias, its value relative to prolonged tape monitoring of the ambulatory patient is debatable and remains to be defined Furthermore, it should be noted that tachycardia and limited lead selection often make detailed morphologic analysis of abnormal beats difficult or impossible

Miscellaneous

Exercise testing has been used to investigate a variety of noncardiac disease states which produce abnormal cardiovascular function An impaired cardiac output response to exercise has been detected in patients with inferior vena caval ligation [115] Measurement of ankle systolic blood pressure during exercise has proved helpful in the diagnosis of peripheral vascular disease [116] Stress testing has also demonstrated that increasing work loads in hemodialysis patients with arteriovenous fistulas and shunts produce disproportionate increases in the hemodynamic load.[117]

Stress testing has provided valuable information regarding the exaggerated and potentially deleterious blood pressure response to static[118] and dynamic[119] exercise observed in hypertensive subjects. It has also been useful in judging the effectiveness of antihypertensive therapy[119,120] and in defining the mechanism of exercise hypotension after sympathetic blockade [121]

Stress testing can also be quite informative in patients complaining of a variety of cardiovascular symptoms without apparent cardiovascular disease Frequently it is concluded that such patients have no cardiovascular basis for their symptomatology Before attributing symptoms of dyspnea weakness or dizziness to emotional factors, however, we usually perform a maximal stress test and, if necessary, use Epstein s protocol[1] to critically assess the hemodynamic response Occasionally the stress test reveals an organic basis for suspected functional complaints, such as an arrhythmia [110] or idiopathic orthostatic hypotension,[112] or discloses an impaired cardiovascular response to exercise consistent with a cardiomyopathy

Conclusion

Exercise stress testing has become a very useful tool in the diagnosis therapy and investigation of all forms of cardiovascular disease Stress testing is most informative when one adheres to the guidelines emphasized above It must be remembered that the exercise protocol itself can influence the results of the test and that the test must be tailored to the individual needs of the subject

Limitation of exercise capacity and abnormal ST segment responses do not always indicate cardiovascular disease Malingering poor motivation anemia pulmonary dysfunction hypovolemia and altered oxygen carrying capacity of hemoglobin are a few of the noncardiac causes of abnormal exercise responses ST segment changes can occur in subjects with normal coronary arteriograms

Exercise testing at the present time is probably most useful in the evaluation of medical and surgical therapeutic interventions. With an increasing number of longitudinal studies and further technical developments the usefulness of stress testing in determining functional classification will improve In turn it will become possible to rely more heavily on the stress test for information regarding the most opportune time for therapeutic intervention

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Experimental and laboratory reports

A videotechnique for recording continuously left ventricular wall motion and changes in wall thickness

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Site extent, and degree of regional myocardial dysfunction in coronary heart disease are considered to be major determinants of left ventricular performance [1,2] Regional myocardial dysfunction can be recognized by high speed cineangiocardiography For its quantitative assessment, however frame by frame analysis is required.[3] Since such an analysis is tedious its usefulness for routine diagnostic procedures is limited. Therefore a device has been developed which permits continuous recording of left ventricular wall motion and changes in wall thickness during the cardiac cycle

Methods

The method is based upon transforming the fluoroscopic or angiographic information into a video signal which is analyzed through an electronic circuit Fig 1 shows a ventriculogram displayed on a television monitor The television screen is composed of a series of horizontal scan lines Variations in light intensity are represented by corresponding changes in voltage amplitude of the video signal The dark left ventricular cavity is expressed through a lower voltage and the bright surrounding tissue by a proportionally higher voltage The left ventricular wall resembles a zone of intermediate intensity It is expressed by a voltage of intermediate amplitude

The three horizontal bars across the left ventricular wall represent electronic windows They are variable in length and can be placed across any portion of the cardiovascular silhouette Each window corresponds to that region of the left ventricular wall from which motion is to be recorded.

Fig 2 depicts the change in voltage amplitude of the video signal while crossing the left ventricular wall The low voltage amplitude to the left reflects the dark opacified left ventricular cavity and the higher amplitude to the right the bright surrounding tissues At the interfaces between the cavity and the inner wall (i) and the outer wall and the surrounding tissues (o) increases in the video sweep voltage are seen to occur By inspecting the video image of the heart two threshold voltages (*L1* and *L2*) are set to the levels at which the video sweep voltages increase at points *o* and *i*, respectively

For recording the movements of the inner and outer borders of the wall a *control* signal (*CS*) is generated. The amplitude of this signal is determined by the amplitude of the video signal (*VS*) during its sweep through the electronic window from left to right. As the video sweep reaches the left hand edge *of* the window a maximum increase of the control voltage occurs (*W*) and is held constant until the video signal reaches the first preset threshold voltage (*L2*) corresponding to the inner border At this point the control sig

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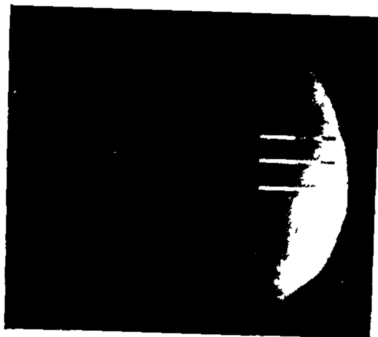


Fig 1 Angiocardiography of the left ventricle as displayed on the television control monitor The three horizontal bars on the right represent the electronic windows and indicate the regions of the left ventricular wall from which motion is recorded Each window contains three zones of different brightness The transition between the zones marks that point in which the inner and outer margin of the left ventricular wall is tracked

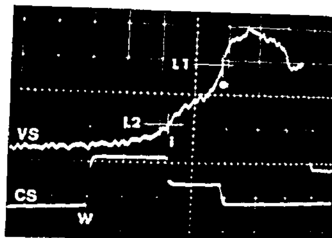


Fig 2 Oscillographic display of the video sweep signal VS while crossing the left ventricular wall. The lower voltage to the left represents the dark opacified left ventricular cavity and the higher voltage to the right represents the bright surrounding tissues. At the inner and outer margin of the left ventricular wall (points *i* and *o*) steep increases in voltage occur The comparator thresholds are set to these levels. The voltage signal *CS* in the lower half is added to the video sweep signal when displayed on the control monitor The steep rise W on the left indicates the beginning of the window Inner and outer margins of the left ventricular wall (*o* and *i*) are marked by steplike decreases and indicate the moment the video signal exceeds *L1* and *L2* respectively

nal decreases to a lower fixed level which is maintained until the video signal exceeds the second preset threshold voltage (*L1*) This is accompanied by a return of the control signal to 0 These changes in amplitude of the control signal can be recognized within the electronic windows by separate zones of different light intensity (see Fig 1) The interfaces *i* and *o* between the three zones represent both points of the heart border which are tracked. By displaying the control signal on the television screen, an accurate fit of the threshold levels can be made with the observed anatomy Finally, from each of the three windows, a tracing is made of the relative location of the inner and/or outer wall borders with respect to the left hand edge of the electronic window These trace signals are derived through separate integration circuits, the outputs of which are proportional to the time duration of the two voltage levels of the control signal and thus proportional to the distance of the inner and outer borders, respectively, from the reference location (i e , the left hand edge of the electronic window) The difference between these signals produces an additional tracing proportional to the wall thickness

Details of the electronic circuit are shown schematically in Fig 3

Since background structures can interfere with accurate tracking of wall motion a so called level correction system is used. It has been described previously[4] and is depicted in Fig 3 In brief linearly changing voltages are added to the horizontal video sweep lines The slope of the voltage change is determined by the examiner according to the change in brightness of background structures While the left ventricular border moves against a background of varying light intensity, the level of which the voltage change occurs can be altered. By addition of an adjustable voltage compensation for the variations in background brightness can be made

Frequency response characteristics of the system were determined by using a generated sine wave In addition an eccentrically rotating radiopaque wheel was recorded through the x ray image intensifier television system and the electronic window placed to the margin of the wheel so that a moving border was produced Application of a generated sine wave produced a response of 100 per cent at 5 c p s , 95 per cent at 10 c.p s and 80 per cent at 20 c p s When the rotating wheel was used there was a response of 90 per cent at 6 5 c p s The linearity of the system was established by recording a grid pattern consisting of 1 by 1 cm squares There was

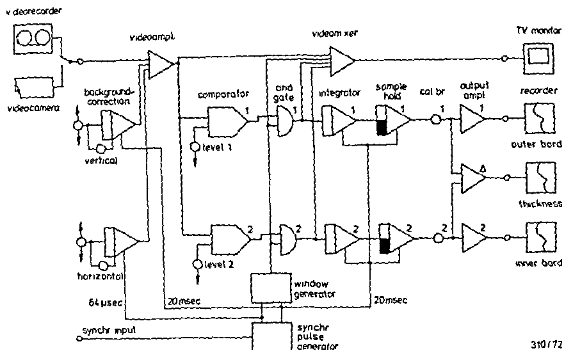


Fig 3 Block diagram depicting the electronic circuit for determining motion of the inner and outer margin of the left ventricular wall and for the background correction system The video signal is obtained from the videocamera or the videorecorder and applied through the videoamplifier to two comparators. Their threshold levels are set to the voltage amplitudes $L1$ and $L2$ The comparator outputs—constant voltage signals—are fed to integrators through gates. Since the gating input is connected to the window generator the comparator signal reaches the integrator only during the time that the video sweep passes through the electronic window and has not exceeded voltages $L1$ and $L2$ respectively Thus the integrator end value for each video sweep is proportional to the spatial distance between the edge of the electronic window and the inner and outer border respectively The integrator end value is held by a sample and hold for the duration of one videoframe while the integrator is reset to 0 before the arrival of the following comparator signal By applying the voltage signals for the inner and outer border to a differential amplifier a signal proportional to wall thickness is obtained. The level correction system consists of two integrators operated by the synchronous pulse generator Ramp pulses are generated at 64 µsec and 20 msec intervals thus corresponding to the duration of one horizontal sweep line and one videoframe respectively and are added in the videoamplifier to the video signal The video signal the signals for the window and the gated comparator output signals are added and displayed on the control monitor

excellent linearity within the center of the television screen but at the edges it fell off by 6 per cent. The response to a generated square wave showed a time lag of 12 msec.

In order to record wall motion or changes in wall thickness the fluoroscopic or angiocardiographic images were stored on video tape* initially On the audiochannel the electrocardiogram (ECG) was recorded as a reference tracing The tracking windows and the comparator thresholds were selected and adjusted to the left ventricular wall on a still picture Before the final recording was made the accurate fit of the windows, the thresholds and the background correction system were checked during a slow motion replay

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Results

Examples of continuous wall motion recordings are shown in Fig 4 They were obtained by fluoroscopy from a healthy subject (K H.) and from a patient with severe coronary heart disease (R H) The tracking sites were the basal the middle and the apical portion of the left ventricular wall The location of the windows is shown schematically in the upper left hand corner The calibration of the system was the same for both recordings In the normal subject wall motion occurs synchronously in all portions although there are differences in amplitude The

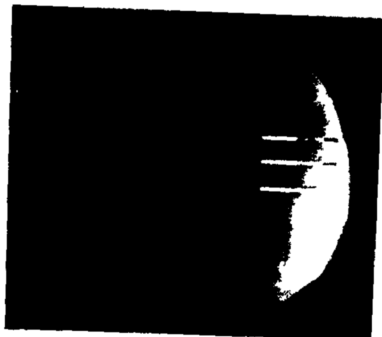


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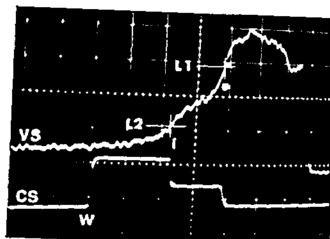


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Frequency response characteristics of the system were determined by using a generated sine wave In addition, an eccentrically rotating radiopaque wheel was recorded through the x ray image intensifier television system and the electronic window placed to the margin of the wheel so that a moving border was produced Application of a generated sine wave produced a response of 100 per cent at 5 c p s 95 per cent at 10 c p s and 80 per cent at 20 c p s When the rotating wheel was used there was a response of 90 per cent at 6 5 c p s The linearity of the system was established by recording a grid pattern consisting of 1 by 1 cm squares There was

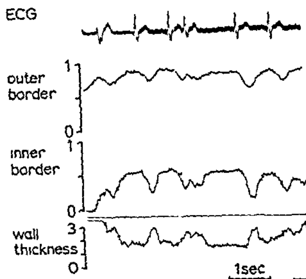


Fig 6 Simultaneous recording of the movements of the inner and outer border of the left ventricular wall during angiocardiography Changes in wall thickness are shown in the bottom tracing

ent system the sudden change in voltage amplitude at the interface between different structures is tracked by a comparator voltage Due to anatomical structures overlapping the cardiac border the level at which the voltage change occurs varies throughout the cardiac cycle Therefore a so called background correction system is used For each study the threshold voltages are determined and the background correction signals adjusted Their accurate fit is checked on the screen of the television monitor

The frequency response and the response time characteristics of the present system compare well with those reported for video and radarkymography In contrast to the response to a generated sine wave applied directly to the measuring circuitry the response to an eccentrically rotating wheel using the image intensifier videocamera videorecorder system was clearly decreased. The major limiting factors therefore reside in the image intensifier videocamera system and in particular in the television scan rate

Similar to video and radarkymography several portions of the left ventricular wall can be examined simultaneously Thus wall motion in various parts of the left ventricle can be easily compared and regional dysfunctions be detected In addition the present system uses two comparator threshold levels for each tracking window which allows to track the inner and outer border of the free left ventricle at the same time and to measure wall thickness in real time"

Degree and time course of changes in wall thickness can be important additional parameters for assessing myocardial function Their measurement may be particularly helpful in detecting regional myocardial disturbances Although wall thickness can be determined by means of ultrasound[10,11] it remains difficult to apply the technique to particular areas of interest. Utilizing the new device any portion of the free left ventricular wall can be selected for analysis

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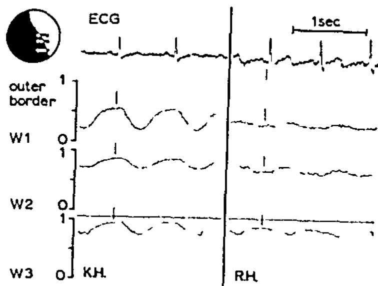


Fig 4. Left ventricular wall motion recording in a healthy subject (K H) and a patient with coronary heart disease (R. H) The location of the tracking windows is shown schematically in the upper left corner While in the normal subject movements occur synchronously in all portions, in the patient with coronary heart disease the two upper tracings show an outward motion during systole The movement recorded from the apical region however follows a normal pattern but is markedly diminished.

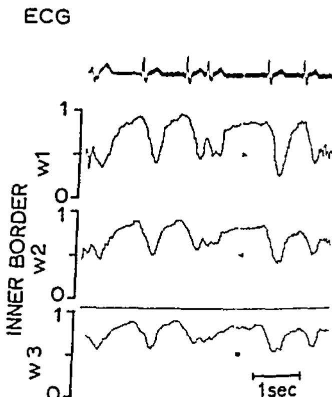


Fig 5 Motion of the inner border of the left ventricular wall during angiocardiography Movements in the three regions occur synchronously and are markedly potentiated during postextrasystolic contractions.

rapid initial downward deflection represents the inward movement of the wall during ejection It is followed by a slower upstroke reflecting the filling period.

In contrast to the normal subject in the patient with coronary heart disease wall motion is clearly different It is diminished in amplitude and differs between the regions studied While the apical region behaves in a normal fashion the basal and middle portions show an initial outward movement during systole

In Fig 5 the movements of the inner border of the free left ventricular wall during angiocardiography are recorded The tracking windows *w1*, *w2*, and *w3* were placed in three different regions Although the three regions differ in amplitude of motion they move synchronously Furthermore, the recording clearly demonstrates the increased inward motion of the left ventricular wall during postextrasystolic contractions

By recording motion of the inner and outer border of the left ventricular wall simultaneously, changes in wall thickness can be measured continuously In Fig 6 movements of the inner and outer border are shown in the middle and upper panels, respectively Wall thickness is recorded in the bottom tracing During the normal contraction wall thickness increases by 52 per cent, while increases of 68 and 86 per cent respectively are noted during postextrasystolic beats

Discussion

Various techniqes have been employed for studying left ventricular wall motion By conventional roentgenkymography it is possible to recognize the extent to which certain structures of the cardiovascular silhouette are moving during the cardiac cycle However it remains difficult to correlate the movements with other hemodynamic events Similarly to videokymography[5,6] and to radarkymography,[7,9] left ventricular wall motion can be tracked continuously by the device described in this report and be related to other hemodynamic parameters

As in videokymography and in radarkymography, the device described here utilizes a video signal and tracks wall motion along the horizontal scan lines While in videokymography the total light intensity within a sampling window is determined in radarkymography the video signal is differentiated The voltage peak at the transition zone from dark to light is followed by means of a track while scan loop With the pres

if administered in a hypoxic Tyrode s solution Data of a typical lidocaine experiment are collected in Table I and qualitatively similar results were obtained in the other experiments In the tabulated experiment, as in the quinidine and procainamide experiment the drug concentration which abolished excitability during perfusion with a hypoxic drug solution also noticeably decreased excitability of the preparation when perfused with an oxygenated solution This however was not the case in the diphenylhydantoin and the two other lidocaine experiments i e concentrations of these drugs which caused no significant depression of the preparation when perfused with oxygenated solution completely abolished excitability when perfused with a hypoxic solution

This selective depression was not dependent upon the superimposition of hypoxia upon drug perfusion since in two experiments the addition of lidocaine (10^{-4}M) to a hypoxic perfusate resulted in inexcitability in less than 12 minutes. In oxygenated solutions this concentration never abolished excitability

The inexcitability could not have resulted from prolonged hypoxia alone since (1) all preparations remained excitable during 15 minute perfusions with hypoxic drug free solution and this also was true for a preparation which had previously been rendered inexcitable by a hypoxic drug solution (2) Trautwein and associates[3] have shown that cardiac tissue tolerates much longer periods of hypoxia (similar pO_2 as in our experiments) and we have confirmed this in another series of experiments (3) the loss of excitability which is recorded in hypoxic drug free solutions occurred at a much slower rate than in the drug containing hypoxic solutions and (4) if upon occurrence of inexcitability in the hypoxic drug solution the preparation was perfused with a drug free hypoxic solution (identical pO_2 as of the hypoxic drug solution) then excitability recovered toward the prehypoxic drug level (Fig 1)

Conversely these effects could not have resulted from prolonged exposure to the antiarrhythmic drugs at these concentrations The evidence for this includes reports by other investigators that, in oxygenated solutions higher concentrations are necessary to observe such depressant effects.[6,4] Also we found in other experiments in oxygenated solutions that higher con-

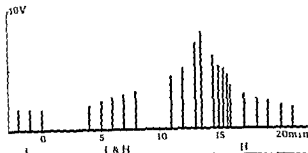


Fig 1 Effects of 10^{-4}M lidocaine (L) lidocaine and hypoxia (L&H) and hypoxia (H) on the threshold stimulation voltage (volts) of a guinea pig papillary muscle

centrations for longer times did not result in inexcitability and, finally if upon occurrence of inexcitability in the hypoxic drug solution the preparation was perfused with an oxygenated drug solution (identical drug concentration) then excitability recovered toward the prehypoxic value

These effects appear not to be species dependent in one dog preparation perfused with hypoxic Tyrode s solution both Purkinje and myocardial cells were rendered inexcitable upon addition of 10^{-5}M lidocaine to the perfusate Other experiments with dog Purkinje and myocardial preparations in oxygenated solutions have shown only slight depression and never loss of excitability at this concentration of lidocaine

Discussion

The above results show that antiarrhythmic drugs selectively depress hypoxic ventricular fibers and this property is common to all tested antiarrhythmic drugs It is conceivable that hypoxia and any other depressant agent could have additive effects. However it is less expected that antiarrhythmic drugs can abolish electrical activity in tissue perfused with a hypoxic solution at the same concentrations which have minimal effect in tissue perfused instead with oxygenated Tyrode s solution (e g the dog experiment) We therefore prefer to use the term selectivity in describing this property rather than refer to it as an additive process

The fact that sometimes high dosages (depressant under control condition) were necessary to abolish electrical activity in the hypoxic preparation can be attributed to the short duration and the degree of hypoxia Indeed, except for the action potential duration the electrical activity of the preparations was not always considerably

Antiarrhythmic drug action Selective depression of hypoxic cardiac cells

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Richard A Jensen Ph D
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Present understanding of the mechanisms by which antiarrhythmic drugs might abolish arrhythmias is based primarily on observations of these drugs on normal cardiac fibers [1,2] The actions of these drugs may well be different in the diseased fibers that are responsible for arrhythmias We have found that quinidine procainamide lidocaine and diphenylhydantoin decreased excitability action potential amplitude and maximum upstroke velocity in hypoxic fibers to a greater extent than in fibers perfused with oxygenated Tyrode's solution

Materials and methods

Papillary muscles of six guinea pigs were mounted in a 3 ml tissue bath which was perfused at a rate of 0 5 L per hour by a Tyrode s solution (NaCl 137 KCl 5, $MgCl_2$ 1 07 NaH_2PO_4 0 457, $NaHCO_3$ 11 9 $CaCl_2$ 1 8 and glucose 5 5 mM) at 37° C and gassed with a mixture of either 5 per cent CO_2–95 per cent O_2 or 5 per cent CO_2 95 per cent N_2 The pO_2 of the hypoxic Tyrode's solutions in the bath ranged from 30 to 80 mm Hg At the start of the experiment the preparations were repetitively exposed (usually about three times) to a zero glucose hypoxic solution until a marked shortening of the action potential duration occurred without delay upon perfusion with hypoxic solutions [3] After this conditioning period the preparations were then perfused with oxygenated Tyrode's solution for at least 30 minutes. The preparations were then perfused alternately with oxygenated and with hypoxic Tyrode's solutions for 15 minute periods to which increasing amounts of drug were added and this sequence was repeated until inexcitability occurred. The preparations were stimulated every 750 msec by a threshold stimulus of 1 msec duration The threshold stimulation voltage (TSV) was read from a precision ten turn potentiometer and expressed as a percentage of the initial control value Standard glass micropipette recording techniques were used.

Results

As previously described by Trautwein and associates[3] we found that hypoxia shortened the action potential duration and decreased the resting potential action potential amplitude and maximum upstroke velocity of the action potential. We further observed that the excitability (1/TSV) initially increased but then decreased[4,5] so that at the end of a 15 minute hypoxic period TSV was either smaller equal, or larger than control values but any increase was always much less than 100 per cent None of the preparations was rendered inexcitable by such 15 minute periods of hypoxia alone

Drugs were tested in concentrations ranging from 10^{-5}M to 2 10^{-4}M These concentrations are normally considered to cover the therapeutic to toxic range [7,8] However, in every preparation there was a drug concentration (lidocaine 10^{-4}M, 2 10^{-4}M and 10^{-4}M in three separate experiments procainamide 8 10^{-5}M quinidine 10^{-5}M and diphenylhydantoin 10^{-4}M) which by itself did not abolish excitability, i e was relatively non toxic but did render the preparation inexcitable

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ic Tyrode s solution All drugs in concentrations which only moderately depressed preparations in oxygenated solutions extensively depressed or abolished electrical activity in preparations in hypoxic solutions It is proposed that antiarrhythmic drugs could act in this way to abolish the electrical activity of the diseased tissue responsible for arrhythmias without extensive depression of the normal tissue

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Table I Lidocaine induced changes in the electrical properties of cardiac fibers perfused with oxygenated (O_2) and hypoxic (N_2) Tyrode's solution

	Control		10^{-5}M		$5 \cdot 10^{-5}$M		10^{-4}M		$2 \cdot 10^{-4}$M	
	O_2	N_2	O	N_2	O_2	N_2	O_2	N_2	O_2	N_2
APD (msec)	111	18	96	16	90	16	88	16	88	18†
DV/DT (V/sec)	280	220	250	200	260	185	280	120	160	<90†
AA (msec)	116	86	112	90	114	88	116	80	106	40†
TSV (%)	100	158	110	184	126	289	136	421	163	596†

APD action potential duration DV/DT maximum upstroke velocity of the upstroke of the action potential AA action potential amplitude TSV threshold stimulation voltage expressed as a percentage of the control value.
†Inexcitability and the values immediately preceding the dagger indicate measurements obtained immediately before inexcitability occurred.

depressed, but even then the effect of these drugs was still considerably more pronounced under hypoxic than under control conditions (Table I)

This property of selective depression was demonstrated at normal potassium concentration (5 mM) and contrasts with the apparently contradictory data of Bassett and colleagues[10] showing a protective action by one of these drugs, diphenylhydantoin This protective effect may be due to the low potassium concentration of the Tyrode's solution (3 mM) and the low drug concentrations used (10^{-8}M to 10^{-7}M) Indeed our laboratory has previously shown that diphenylhydantoin has consistently depressant effects at what is considered to be normal potassium concentrations[11,12] Also Singh and Vaughan Williams[8] showed that diphenylhydantoin has only antidepressive activity if low potassium (3 mM) was combined with drug concentrations smaller than the therapeutic range (10^{-5}M to 10^{-4}M) In another series of experiments we confirmed the findings of Bassett and his colleagues[10] that in 3mM potassium the maximum antidepressive response occurs at 10^{-8}M to 10^{-7}M diphenylhydantoin

In the present experiments we studied the effects of commonly used antiarrhythmic drugs on ventricular tissue perfused with hypoxic Tyrode's solution This allowed us to investigate the possibility that these drugs may have different effects under the type of abnormal conditions that may lead to arrhythmias Hypoxia was used as an experimental variable since similar changes occur during hypoxia and during ischemia, a condition which is clinically frequently associated with arrhythmias Indeed, hypoxia and ischemia both shorten the effective refractory period and the duration of the action potential decrease the resting potential the action potential amplitude and the maximum upstroke velocity, and initially increase and then progressively decrease excitability[1,3,4,5] Also many of the metabolic alterations during hypoxia and ischemia are changed in a similar fashion[13] The electrophysiologic changes observed during hypoxia can be reversed by perfusing the tissue with 50 mM glucose[14] and similar beneficial effects could be expected in ischemic tissue by maximally stimulating glycolysis[13] This evidence suggests that many of the changes observed during hypoxia and ischemia are due to the lack of energy[15]

Because of the electrophysiologic and metabolic similarities between hypoxia and ischemia it is tempting to propose that in vitro hypoxia may represent a reasonable model for in vivo ischemia Antiarrhythmic drugs could then abolish re entrant arrhythmias due to ischemic lesions by transforming the unidirectional block (a prime requirement for re entry[9]) to a bidirectional block Since the depressant action is selectional, i e, most pronounced in the hypoxic tissue these drugs could abolish a unidirectional block in the diseased area without transforming bidirectional conduction into unidirectional block in the normal or less affected area

Summary

A comparison has been made of the effects of commonly used antiarrhythmic drugs on the electrophysiologic characteristics of ventricular cardiac fibers perfused by oxygenated and hypox

of the heart and along the Z axis of the body After the electrodes were placed in the ventricular myocardium the shaft was fixed on a supporting rod (R in Fig 1) which fixed the position of the heart After positioning the three pairs of electrodes the chest wall was closed tightly enough to maintain pressure of −3 to −5 cm of H_2O by continuous aspiration through a polyethylene tube (T in Fig 1) Sinusoidal currents (20 Hz) were fed from an oscillator (Hewlett Packard 204B) between each pair of electrodes and they were used as dipoles generating potential fields in the X (X dipole) Y (Y dipole) and Z (Z dipole) directions of the canine body The strength of the current (about 50 μA) was adjusted low enough to avoid ventricular premature beats

Recording The electrical signals on the body surface generated from the dipoles were recorded with the McFee Parungao lead system[21] and fed to preamplifiers with a band pass filter (5 6 ∼ 30 Hz) The electrocardiograms were also recorded similarly but through amplifiers with a filter of a different band pass frequency (0 56∼100 Hz) These amplifiers were connected to a 6 channel direct visual photorecorder (Yokogawa Electric EMO 62) which served for simultaneous recordings of the signals from the dipoles and the electrocardiograms The overall sensitivity of the recording system was adjusted to 1 cm per microvolt (cm/μV) for the signals generated from the dipoles and 1 cm per millivolt (cm/mV) for electrocardiograms The polarity of the recording system was arranged so that the positive potentials on the left foot and front sides produce an upward deflection in Leads X Y and Z respectively

Results

Most of the 73 dogs showed an R or Rs pattern in Leads X and Y and an RS pattern in Lead Z In 17 out of the 73 dogs there was no appreciable alteration in the QRS duration before and after the dipoles were implanted on either the anterior (9 out of 17) or posterior wall (8 out of 17) of the ventricles. In these dogs the orientation of the three dipoles was tested by recording with the McFee Parungao lead system When the X dipole was generated, the signals in Lead X were at least 10 times greater than those in Leads Y and Z, as is seen in Fig 4 A and vice versa when the Y or Z dipole was generated (not shown)

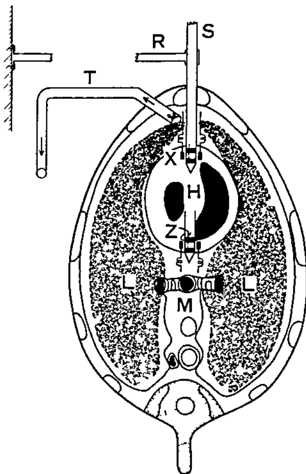


Fig 1 Schematic illustration of the experimental set up The thorax of the dog is shown in a horizontal section through the heart H heart L lung M posterior mediastinum X. X dipole Z Z-dipole S steel shaft R holding rod T aspiration tube

Therefore the three pairs of dipole on either the anterior or posterior wall appeared to be correctly placed along the X Y and Z axes The electrical potential in Lead X generated from the X dipole on the anterior or posterior wall of the ventricles was compared with the R wave in Lead X, while the lungs were over inflated. Similar comparisons with the R and S waves in Leads Y and Z were made for the potentials generated from the Y and Z dipole respectively The following nomenclature will be used for the potentials generated on the body surface from the dipoles and for the R and S waves in Leads X, Y and Z

Dxa = the potential in Lead X from the X dipole on the anterior wall.

Electrocardiographic changes in pulmonary emphysema Effects of experimentally induced over-inflation of the lungs on QRS complexes

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Several characteristic changes of the QRS complexes have been reported in patients with pulmonary emphysema [1-12] In these clinical studies the reduced electrical conductivity in the lungs was considered as the probable cause of the changes in the QRS complexes [1,6,8,12] However the influence of the electrical conductivity of the lungs to cardiac potentials on the body surface is not yet established experimentally [13-20] Flaherty and co workers[18] demonstrated some changes in cardiac potentials on the body surface during respiration which might be attributable to fluctuation in the electrical conductivity in the lungs and/or to positional alteration of the heart during respiratory movement. In dogs with an electrical dipole implanted in the thoracic cage Pownsner Nahum and Mauro[15] stressed the effect of positional change of the dipole rather than that of the electrical conductivity of the lungs, on respiratory fluctuation in the potentials from the dipole distributed on the body surface

We attempted to study the effects of experimentally induced over inflation of the lungs upon the electrical signals transmitted to the body surface from an artificial generator compared with the effects upon the QRS complexes of the electrocardiogram The electrical signals changed in close correlation with the QRS complexes during over inflation of the lungs The changes in QRS complexes induced by over inflation of the lungs resembled those in pulmonary emphysema, and appeared to be related to the influence of the emphysematous lungs on the QRS changes in pulmonary emphysema

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Methods

Preparation Seventy three mongrel dogs (10 to 15 kilograms body weight) were anesthetized by intravenous injection of sodium pentobarbital (30 mg per kilogram) In the supine position the thoracic cage was opened midsternally under artificial respiration and the heart exposed The tidal volume for each stroke of a respirator was adjusted to 150 ml Over inflation of the lungs was experimentally induced by blocking the exhaust of the respirator Thus the lung volume was increased by 150 ml for each stroke of the respirator

Setting of dipoles Two pairs of bipolar electrodes consisting of rectangular platinum plates (5 mm by 3 mm) with an interpolar distance of about 1 cm and with the orientation along the X (X in Fig 1) and Y axes of the body (not illustrated) were placed on the anterior or posterior wall of the ventricles An additional pair of electrodes (Z in Fig 1) comprised two platinum rings (3 mm wide) attached on an insulated steel shaft (5 mm in diameter and 30 cm in length) (S in Fig 1) with an interpolar distance of 5 mm The shaft was advanced into the ventricular septum in a direction rectangular to the anterior surface

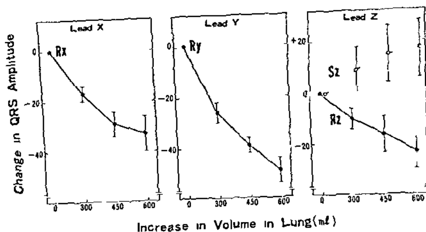


Fig 3 Effects of over inflation of the lungs on QRS amplitude The mean of Rx, Ry Rz and Sz for the 17 dogs were plotted as per cent change from the control (ordinate) against increase in volume of the lungs (abscissa) Closed circles for Rx Ry and Rz and open circles for Sz. Vertical bars indicate standard deviation

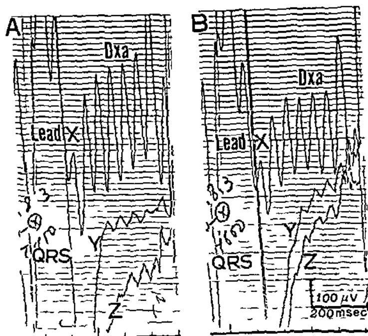


Fig 4 Examples of potentials generated from the X dipole The signals generated from the X dipole on the anterior wall of the ventricles were recorded with Leads X, Y and Z in superposition with the electrocardiograms A major part of the QRS complexes are scaled out of the records *A* without inflation of the lungs *B* with inflation of the lungs by 600 ml.

sion of the lungs by 600 ml There were similar reductions in Dya and Dza (not illustrated) On the other hand, in the remaining eight dogs with the three dipoles on the posterior ventricular wall there were divergent changes in the potentials generated from the dipoles an increase in Dzp and a decrease in Dxp and Dyp Average changes in the amplitudes of the potentials generated from the dipoles are shown in Fig 5 for the nine (closed circles) and eight dogs (open circles) with anterior and posterior dipoles respectively Both Dxa and Dxp generated from the dipoles on the anterior and posterior walls of the ventricles exhibited a reduction of about 30 per cent from the control for expansion of the lungs by 600 ml, roughly equalling the reduction

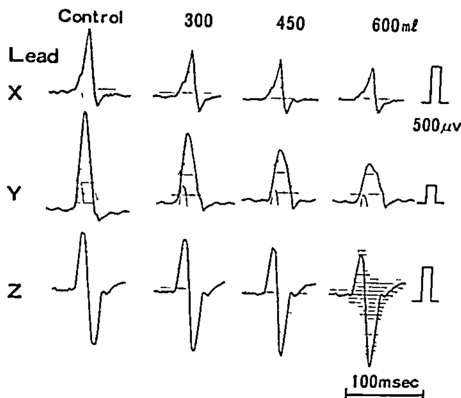


Fig 2. Changes in the QRS complexes induced by over inflation of the lungs. The QRS complexes of Lead X during control and during over inflation of the lungs are shown in the top row Those of Leads Y and Z are in the second and third rows The amount of over inflation is indicated above the top row Calibrations of 500 μV and a time scale of 100 msec apply to all records. The positive potentials on the left, foot and front sides give upward deflections

Dxp = the potential in Lead X from the X dipole on the posterior wall
Dya = the potential in Lead Y from the Y dipole on the anterior wall
Dyp = the potential in Lead Y from the Y dipole on the posterior wall
Dza = the potential in Lead Z from the Z dipole on the anterior wall
Dzp = the potential in Lead Z from the Z dipole on the posterior wall
Rx = the R wave in Lead X
Ry = the R wave in Lead Y
Rz = the R wave in Lead Z
Sz = the S wave in Lead Z

Changes in QRS amplitudes The changes in the QRS complexes during experimentally induced over inflation of the lungs are demonstrated in Fig 2 With an increase in the volume of the lungs there was a reduction in the amplitude of Rx It reduced to about 50 per cent of the control after the expansion of the lungs by 600 ml (compare the records of the extreme left and right in the top row) A comparable amount of reduction was also found in the amplitude of Ry (the middle row in Fig 2) There was a similar reduction in the amplitude of Rz though less prominent than those in Rx and Ry In contrast, there was a tendency that Sz increased as the lungs were expanded The increase was about 30 per cent above the control for expansion of the lungs by 600 ml (compare the records of the extreme left and right in the bottom row) These changes in the QRS complexes during over inflation of the lungs were analyzed for the 17 dogs. In Fig 3 average changes of the R (closed circles) and S waves (open circles) in Leads X, Y, and Z are represented The reduction in the amplitude of Rx was 17 29, and 33 per cent of the control for expansion of the lungs by 300 450 and 600 ml Corresponding changes were 26 39, and 49 per cent for Ry and 10, 16, and 23 per cent for Rz. The increase in the amplitude of Sz was 9, 15 and 17 per cent

Changes in the potentials generated from the dipoles Corresponding to the changes in the QRS complexes Dxa Dya and Dza were all reduced in the nine dogs with the three pairs of dipoles implanted on the anterior wall Fig 4 represents an example of changes in Dxa induced by expansion of the lungs by 600 ml Dxa is reduced to about half of the control after expan

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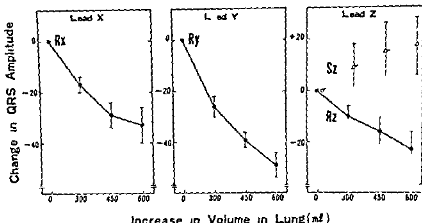


Fig 3 Effects of over inflation of the lungs on QRS amplitude. The mean of Rx, Ry Rz, and Sz for the 17 dogs were plotted as per cent change from the control (ordinate) against increase in volume of the lungs (abscissa) Closed circles for Rx Ry and Rz, and open circles for Sz. Vertical bars indicate standard deviation.

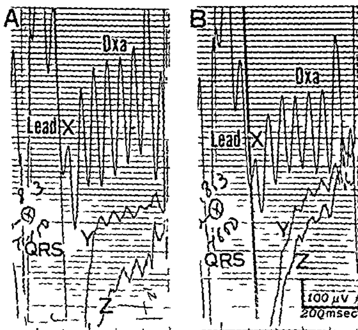


Fig. 4 Examples of potentials generated from the X-dipole The signals generated from the X dipole on the anterior wall of the ventricles were recorded with Leads X, Y and Z in superposition with the electrocardiograms A major part of the QRS complexes are scaled out of the records A, without inflation of the lungs B, with inflation of the lungs by 600 ml.

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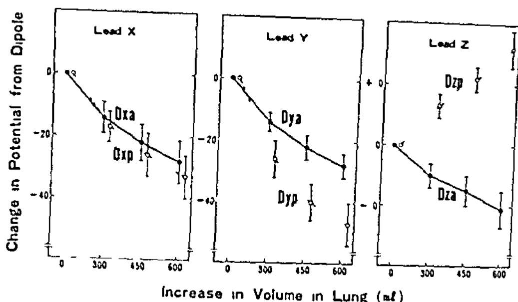


Fig 5 Effects of over inflation in the lungs on the amplitudes of the potentials generated from the dipoles. Closed circles represent the mean values of the potentials generated from the dipoles on the anterior wall of the ventricles (Dxa, Dya, and Dyz) for nine dogs. Open circles represent those of the potentials from the dipoles on the posterior wall (Dxp Dyp and Dzp) for eight dogs. Ordinates amplitudes of the potentials represented as a per cent change from the control Abscissa. increase in volume of the lungs.

in the amplitude of Rx (33 per cent, Fig 3) Similarly, Dya and Dyp exhibited a reduction of about 40 per cent which again corresponds with the reduction in the amplitude of Ry (49 per cent, Fig 3) There were contradictory changes, however between Dza and Dzp Dza was reduced by 21 per cent for expansion of the lungs by 600 ml, while Dzp was increased by 32 per cent, which roughly corresponds to the decrease in Rz (23 per cent, Fig 3) and the increase in Sz (17 per cent Fig 3), respectively

Correlation between the QRS amplitudes and the potentials generated from the dipoles In view of a close relationship of the changes in the R and S waves with those in the potentials generated from the dipoles correlation plots were constructed in Fig 6 of the amplitude of the R or S wave (ordinate) against that of the dipole potential in each of Leads X Y, and Z (abscissa) As indicated by regression lines calculated for the plots, there seems to be good correlations between the R waves (Rx, Ry, and Rz) and the potentials generated from the dipoles on the anterior wall of the ventricles (Dxa Dya, and Dza) Between Rx and Dxa (Fig 6, A), between Ry and Dya (Fig 6,B), and between Rz and Dza (Fig 6,C) correlation coefficients were 0 89 0 80, and 0 90, respectively Similar correlations were found between the R and S waves (Rx, Ry, and Sz) and the potential generated from the dipoles on the posterior wall Correlation coefficients between Rx and Dxp (Fig 6 D), between Ry and Dyp (Fig 6 E), and between Sz and Dzp (Fig 6,F) were 0 80 0 90, and 0 80, respectively

Discussion

The QRS complexes in pulmonary emphysema without cor pulmonale [9 12] are characterized by (1) reduced R waves in the left precordial leads or Lead X of the orthogonal leads, (2) low amplitudes in the standard limb leads or the frontal QRS loop (3) superior displacement, and (4) posterior displacement of the mean QRS axis or the maximum QRS vector All of these findings were experimentally reproduced during over inflation of the lungs The first finding corresponds to the reduction of Rx, the second finding to the simultaneous reduction of Rx and Ry, the third finding to a greater reduction of Ry than of Rx and the last finding with an increment in Sz and a decrement of Rz. Possible causes of these changes are (1) downward displacement of the diaphragm or clockwise rotation of the heart, (2) altered sequence of excitation due to the hemodynamic overload on the right ventricle, and (3) distorted intrathoracic potential fields caused by increased electrical resistance from the heart to the body surface across the over inflated lungs. Since the position of the ventricles was deliberately fixed in the present experiment, the first cause can be rejected. The second cause cannot explain the changes in the potentials

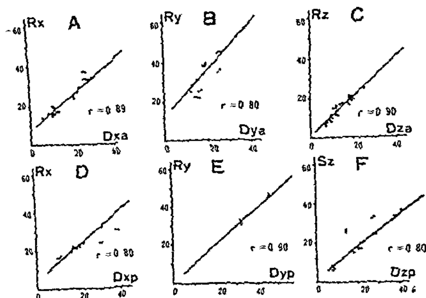


Fig 6 Correlation between the amplitudes of QRS complexes and potentials generated from the dipoles. *A* through *C*, correlations between R waves in Leads X, Y and Z (Rx, Ry and Rz) and potentials generated from the X Y and Z-dipoles on the anterior wall of the ventricles (Dxa Dya and Dza) respectively *A*, between Rx and Dxa *B* between Ry and Dya, and *C* between Rz and Dza *D* through *F* similar diagrams but between R and S waves in Leads X, Y and Z (Rx, Ry and Sz) and potentials from the dipoles on the posterior wall (Dxp Dyp and Dzp) *D* between Rx and Dxp *E* between Ry and Dyp and *F* between Sz and Dzp

generated from the dipoles, because the signal source of the dipoles is independent of over infla tion of the lungs Thus, the third cause remains as a sole factor responsible for the changes in the potentials generated from the dipoles. The decrease in the amplitude of the potentials evoked from the majority of the dipoles (Dxa Dxp Dya Dyp and Dza in Fig 5) may be at tributed to increased electrical resistance be tween the dipoles and the body surface across the over inflated lungs A close correlation between the reductions in the potentials generated from the dipoles (Dxa Dxp Dya Dyp and Dza) and R waves in Leads X, Y and Z (Rx Ry and Rz) in dicates that the reduction in R waves may be ex plained in the same way as the reduction in the potentials generated from the dipoles In spite of the general tendency that both the potentials generated from the dipoles and R waves were reduced during over inflation of the lungs, it is remarkable that the potential generated from the Z-dipole on the posterior wall (Dzp) is con comitantly increased with the S wave in Lead Z (Sz) The increase in Dzp may also be explained by assuming increased resistance across the over inflated lungs. This increase in the resis tance of the lungs which envelop the heart ex cept at the posterior mediastinum will increase the currents which are generated from the Z dipole on the posterior wall of the ventricles and pass through the posterior mediastinum back wards to the posterior body surface This increase of the currents passing toward the posterior body surface will augment Dzp The above view is sup ported by our recent study[22] which revealed in creased current density at the site analogous to the posterior mediastinum where the lung tissue does not intervene between the body surface and the heart The increment in Sz may be explained similarly because cardiac currents responsible for Sz may be generated from the excitation front in the posterior ventricular wall in the final stages of depolarization.[23-25]

In conclusion all changes found in the poten tials generated from the dipoles and the QRS complexes during the experimentally induced over inflation of the lungs can be explained by the single assumption of increased electrical resistance across the lungs. Increased electrical resistance in the inflated lungs has been demon strated in several reports[26-28] Considering the close similarity in the changes of the QRS com plexes between the experimental over inflation of the lungs and pulmonary emphysema it ap

al

pears that the increased electrical resistance across the lungs may be a major cause of the QRS changes of electrocardiograms in pulmonary emphysema

Summary

Seventeen dogs were anesthetized with sodium pentobarbital In these dogs, over inflation of the lungs was experimentally induced by blocking the exhaust of a respirator Dislocation of the heart during over inflation of the lungs was prevented by fixing the heart on a supporting rod.

Three pairs of bipolar electrodes were implanted either on the anterior or posterior wall of the ventricles. They were used as the X (left to right), Y (foot to head) and Z (front to back) dipoles while passing alternating currents (50 μA, 20 Hz.) The electrical signals generated from these dipoles were recorded with the McFee Parungao lead system The same lead system was used for recording electrocardiograms The effects of the over inflation of the lungs upon the potentials generated from the dipoles and upon the QRS complexes of the electrocardiograms were investigated. Potentials generated from the X dipole on the anterior or posterior wall decreased during over inflation of the lungs, in parallel with the R wave in Lead X. Similar reduction was found between the potentials generated from the Y dipole on the anterior or posterior wall and the R wave in Lead Y In contrast opposite changes were found between the potentials generated from the Z dipole on the anterior or posterior wall There was a decrease of the potential generated from the Z dipole on the anterior wall and an increase of that from the Z dipole on the posterior wall Similar contradictory changes were found between the R and S waves in Lead Z The parallelism between changes in the potentials generated from the dipoles and the R and S waves of three orthogonal leads was found to be statistically significant (correlation coefficients $\geq 0\ 80$ Since the position of the heart was fixed, the changes in the potentials generated from the dipoles induced by over inflation of the lungs could be attributed to the increased electrical resistance of the lungs The same explanation may be applied to those changes in the R and S waves which were closely related to the changes in the potentials generated from the dipoles On the basis of resemblance of the changes in the QRS complexes between pulmonary emphysema and the experimentally induced over inflation of the lungs, increased resistance of the lungs may contribute to changes in QRS complexes in pulmonary emphysema

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Immunological identification in plasma of mitochondrial and cytoplasmic aspartate transaminase isoenzymes during experimental myocardial infarction

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The release of aspartate transaminase (AT), (known also as GOT), (L aspartate 2 oxoglutarate aminotransferase, E C 2 6 1 1) into the circulatory system during acute myocardial infarction was first demonstrated by La Due, Wróblewski, and Karmen [1] Borst and Peeters[2] reported the presence of two aspartate transaminases in ox, pig, and rat hearts one contained in mitochondria and the other in the cytoplasmic fraction Recently we described the crystallization of these two isoenzymes from dog heart and the preparation of their specific antibodies [3] The present work was done to determine, by an immunologic technique which form of the aspartate transaminase isoenzyme is liberated into the bloodstream after ligation of the left descending coronary artery and to ascertain the relation between the pattern of the isoenzyme changes in plasma and the epicardial electrocardiographic signs of myocardial infarction

Materials and methods

Ten apparently healthy mongrel dogs weighing 11 to 21 kilograms, were anesthetized with 30 mg per kilogram of body weight of sodium pentobarbital intravenously Respiration was maintained during surgery with a Palmer pump attached to an endotracheal tube The heart was exposed through a lateral anterior incision following the fourth left intercostal space The descending branch of the left coronary artery was dissected free and ligated in one stage near its origin Electrocardiographic unipolar records were obtained by placing the exploring electrode at six different points over the anterior aspect of the left ventricle [4] A first series of tracings was taken 30 minutes after the arterial occlusion The animals were kept anesthetized all the time with sporadic intraperitoneal injections of pentobarbital (128 mg) and the thorax was reopened 48 hours after arterial ligation in order to take a second series of epicardial tracings and to excise the heart.

All dogs received a 10 per cent glucose solution through the femoral vein (15 ml per minute) continuously and a commercial mixture of benzathine, potassium and procaine penicillin G was injected intramuscularly before surgery and 24 hours later

Femoral arterial blood samples were obtained prior to opening the thorax and then every 10 to 12 hours after coronary artery occlusion Plasma was immediately separated from the blood received in heparin and stored at 4° C

A group of six sham operated dogs was also studied (control dogs) The surgical procedure and the 48 hour postoperative handling were similar to those procedures applied to the experimental animals except for the coronary artery ligation and the opening of the pericardial sac

Antibodies against cytoplasmic or mito

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Table I Total cytoplasmic and mitochondrial aspartate transaminase in plasma of dogs with experimental myocardial infarction (maximum levels and times at which they were observed)

Dogs No.	*Time (hr)*	*Total activity (units/mL)*	*Time (hr)*	*Cytoplasmic isoenzyme (units/mL)*	*Time (hr)*	*Mitochondrial isoenzyme (units/mL)*
1	30	750	30	475	30	256
2	20	75	20	88		0
3	10	123	10	93		0
4	24	325	24	319	24	36
5	12	870	12	837	36	245
6	12	400	12	310	24	150
7	12	450	12	375	24	56
8	12	287	12	232	48	25
9	24	775	24	575	24	220
10	12	34[illegible]	12	325	48	44

Samples taken 10 20 30 and 48 hours after coronary artery ligation.

chondrial dog aspartate transaminase isoenzymes were obtained from serum of immunized rabbits[3] and semipurified according to the Na_2SO_4 fractionation technique used by Kekwick[5] to isolate normal human gamma globulin. No cross reaction was observed between the mitochondrial and cytoplasmic isoenzymes. Antibody preparations were tested with crystallized transaminases to establish suitable conditions for a full recovery of the isoenzyme activity in the supernatant when the antibody was not against it and to precipitate the enzyme completely with the specific antibody. The precipitin reaction was estimated quantitatively by mixing 0 40 ml of plasma 0 05 ml of NaCl isotonic solution and 0 05 ml of specific anti isoenzyme globulin solution (approximately 0 15 mg of cytoplasmic or 0 50 mg of mitochondrial anti isoenzyme protein). The mixture was incubated at 37 C for 30 minutes and then was left to stand for 48 hours at 4 C. Afterward the tubes were centrifuged at 0° C for 1 hour at 10 000 × g and the transaminase activity was measured in 0 1 0 2 or 0 3 ml of supernatant fluid. Control mixtures were prepared with rabbit normal gamma globulin. Total cytoplasmic and mitochondrial aspartate transaminase activities were measured in plasma samples incubated with normal gamma globulin antimitochondrial and anticytoplasmic globulins respectively.

Aspartate transaminase activity was estimated spectrophotometrically.[3] One Karmen unit is defined as the amount of enzyme which produces an absorbance fall of 0 001 per minute under the assay conditions.

Results

The arterial plasma concentrations of the total aspartate transaminase activity varied from 10 to 60 Karmen units per milliliter (20 ± 15 average ± S D) in all anesthetized dogs before surgery and all this activity reacted immunologically as cytoplasmic isoenzyme.

In the six animals used as control animals only signs of ischemia (negative T wave) were observed in the 48 hour electrocardiogram. The level of the total transaminase activity in their plasma did not exceed 125 units per milliliter and apparently all of this enzyme was of the cytoplasmic form. The amounts of mitochondrial isoenzyme in some of these dogs were no more than 10 units per milliliter which we consider insignificant under the conditions of our test.

In the 10 experimental dogs the maximum level in plasma of the total aspartate transaminase was usually observed in samples taken 10 to 30 hours after the coronary artery ligation. In a group of eight of these dogs the concentration reached more than 287 units per milliliter. The cytoplasmic isoenzyme represented the major proportion of the total activity and the mitochondrial form appeared at concentrations higher than 25 units per milliliter. No relationship was observed between the level of mitochondrial isoenzyme and the total transaminase activity in plasma. The maximum rise of the two isoenzymes was recorded at the same time in three dogs whereas in five of the dogs the peak mitochondrial form appeared 12 to 36 hours after the maximum cytoplasmic rise (Table I, Figs 1 2 and 3). In the other group of two dogs

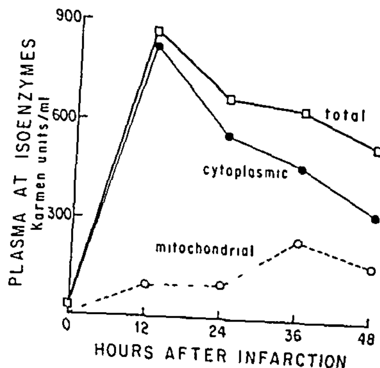


Fig 1 Dog 5 with very high concentrations in plasma of both cytoplasmic and mitochondrial *aspartate transaminase* isoenzymes and electrocardiographic patterns of extensive transmural necrosis. AT = aspartate *transaminase*

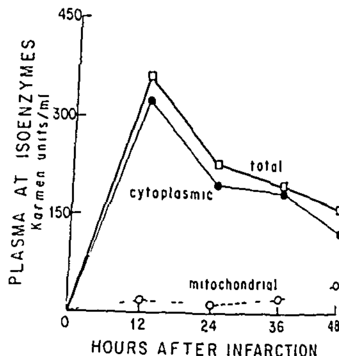


Fig 2 Dog 10 with a moderately high concentration of cytoplasmic isoenzyme in plasma and low levels of mitochondrial activity Moderate though extensive subepicardial injury and extensive subendocardial and circumscribed transmural necrosis AT = aspartate transaminase

(Nos 2 and 3) the levels of total transaminase were as low as those measured in the sham operated animals and mitochondrial isoenzyme was not detected in their plasma

The amount of anti isoenzyme globulin was enough to precipitate up to 400 or 160 Karmen units of cytoplasmic or mitochondrial transaminase under the conditions used in the precipitin reaction The sum of the two isoenzyme activities determined separately was roughly the same as the total activity measured in the presence of normal gamma globulin as it is observed in the values shown for samples of plasma corresponding to the same time of bleeding (Table I)

The myocardial infarcted area in each dog was evaluated electrophysiologically through the 48 hour epicardial tracings and the conclusions must be regarded as a satisfactory qualitative estimation of the grade and extension of myocardial damage Injured tissue was indicated by the presence of RS T displacement subendocardial necrosis was diagnosed by pathologic Q waves (wide and slurred) and transmural necrosis by QS complexes (Table II)

Discussion

Our results demonstrate that, after occluding the left descending coronary artery cytoplasmic aspartate transaminase increased remarkably in the blood of those dogs which showed electrocardiographic signs of injury and necrosis

The presence of mitochondrial isoenzyme in the blood was apparent only in those animals with electrocardiographic signs of necrosis and with maximum levels of total transaminase activity higher than 287 units per milliliter which are equivalent to a myocardial damage of at least 20 per cent of the total cardiac mass calculated according to the correlation found by Agress and co workers [6] In general, the higher levels of mitochondrial form were observed when the necrosis was extensive and transmural

The high proportion of the cytoplasmic isoenzyme found in the blood of dogs with myocardial infarction agrees with the observation of Huzino and co workers[7] who showed a remarkable loss of this isoenzyme and a slight change of the mitochondrial form in infarcted myocardial tissue However these authors failed to detect mitochondrial isoenzyme activity in serum probably because the DEAE cellulose chromatographic method they used is not as sensitive as our immunologic assay Even though partially purified isoenzymes of both the cytoplasmic and mitochondrial extracts from various tissues (liver, kidney, and muscle) were

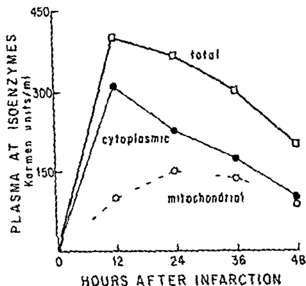


Fig 3 Dog 6 with cytoplasmic isoenzyme concentrations similar to Dog 10 but with a higher percentage of mitochondrial activity The electrocardiographic pattern was similar to that of Dog 5 AT = aspartate transaminase

precipitated by the corresponding rabbit antibodies to the crystallized isoenzymes of dog heart[5] we may assume that in the present experiments the isoenzymes which appeared in the blood were associated with the myocardial infarcted tissue since the cytoplasmic isoenzyme levels were lower and the mitochondrial isoenzyme peak was insignificant in the plasma of control dogs In relation to the relative lateness in the appearance of the mitochondrial isoenzyme peak in plasma we found in a previous work[8] that biochemical and ultrastructural alterations which were apparent in mitochondria isolated from infarcted cardiac tissue 30 minutes after the coronary artery occlusion became more important by the twelfth hour

It is reasonable to suggest that appearance of mitochondrial aspartate transaminase in the blood could be expected in human patients with electrocardiographic signs of necrosis and that a high ratio of this isoenzyme could be related to extensive cardiac transmural necrosis

Summary

Rabbit specific antibodies against cytoplasmic and mitochondrial aspartate transaminase crystallized from dog hearts were used to identify these isoenzymes in blood plasma of dogs after ligature of the left descending coronary artery

Table II Electrocardiographic findings from six points on the left ventricle anterior aspect 48 hours after coronary artery occlusion

Dogs No	*Findings*
2 3	Slight or moderate circumscribed, subendocardial or subepicardial injury
8	Moderate subepicardial injury and circumscribed sub endocardial necrosis.
4	Marked subepicardial injury and extensive subendocardial necrosis.
10	Moderate though extensive subepicardial injury and extensive sub endocardial and circumscribed transmural necrosis.
1 5 6 7 and 9	Slight or moderate, circumscribed or extensive subendocardial injury and extensive transmural necrosis.

Myocardi l lectrophysiologic injury was qualified as sl ght, moderate r marked according to the grade of the RS–T segment di placem nt. Necrosis and injury w re considered extensive or circumscribed if the pecul ar trac ng appeared in all or in som of the six ep cardial points expl red.

Transaminase activity was measured in the supernatant fluid after incubation of plasma with the specific anti isoenzyme antibodies The cytoplasmic isoenzyme always constituted all or the major portion of the total aspartate transaminase activity present in plasma and its maximum level was observed ten to thirty hours after coronary artery occlusion The mitochondrial isoenzyme appeared in the plasma in those animals which showed electrocardiographic signs of necrosis and the mitochondrial isoenzyme tended to be present in greatest quantities when the necrosis was extensive and transmural

The interpretations of the electrical records were done by Alfredo de Micheli M.D., and Demetrio Sodi Pallares M D according to the criteria of the Department of Electrocardiography Instituto Nacional de Cardiologia Mexico City The authors express their thanks to Miss Ofelia Rojas for technical assistance and to Misses Virginia Miranda and Carmen Briones for secretarial services

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The phase plane cardiogram preliminary findings on a healthy population

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The phase plane cardiogram (PPC) the x y display of voltage against its corresponding time derivative (dv/dt) was first introduced by Freeman and co workers[3] These preliminary studies indicated significant differences between the PPCs of healthy individuals and those of individuals with left ventricular hypertrophy

Further studies by this laboratory have shown that the PPC can significantly enhance the slurring (a slope change of the primary voltage excursion) and notching (a momentary directional change of the primary voltage excursion) patterns inherent in the QRS complex of the electrocardiogram (ECG) wave form[3,4] Notching and slurring of the ECG have been correlated with myocardial infarction myocardial fibrosis and certain intraventricular conduction defects[1,2,5,7,9,11] However little emphasis has been placed on the notching and slurring patterns during routine clinical cardiographic interpretation One reason is that such events occur too rapidly or without sufficient magnitude to be consistently reproduced on the standard ECG The PPC has the ability to enhance these small changes therefore facilitating cardiographic analysis Characterization of the notching and slurring patterns could thus increase the diagnostic capability of the ECG

For the characterization of abnormal PPC patterns it is essential to be able to differentiate between abnormal and normal patterns. In order to effectively separate these patterns it is important to establish a reliable normal data base with which comparisons can be made A reliable normal data base requires data collection from a large population of healthy individuals and the capability of analyzing this data Thus the preliminary findings on a normal population and the methods of analyzing these data are being reported.

Methods

The PPC technique utilized the standard 12 lead configuration for signal input. The patient input signal was determined with a lead selector switch (Harvard Apparatus Co) coupled to the input follower stage of a low level preamplifier (Tektronix FM 122) The FM 122 provided a gain of approximately 1 000 with upper and lower frequency filters With the upper frequency filter set at 250 Hz the upper frequency response was 3 db down at 450 Hz and 6 db down at 1 000 Hz. The lower frequency cutoff was set to 0 07 Hz. This band width was less than that encountered in high frequency electrocardiography (HFE) (i e HFE usually better than flat to 1 000 Hz) The band width selected for the PPC allowed adequate signal reproduction with an optimal signal to noise ratio It may be noted, parenthetically that high frequency interference and noise becomes a serious problem since the derivative enhances the higher frequency signals (viz. $dv/dt = V_m \omega Cos_{\omega t}$ where $W = 2\pi f$)

The PPC and the standard scalar ECG were

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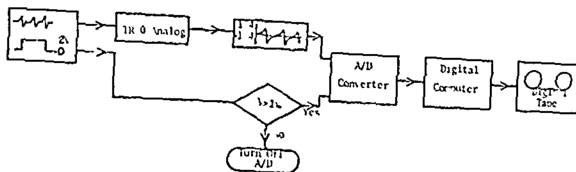


Fig 1 Overall arrangement for computer analysis of data.

displayed on channels 1 and 2 respectively, *of a* dual trace oscilloscope (Tektronix RM561A) Channel 1 of the RM561A was used as an *x y* plotter by utilizing two dual trace amplifiers (Tektronix Type 3A72) i e one in the horizontal (x) axis and one in the vertical (y) axis The PPC was obtained by placing the input voltage (V) on the vertical axis and the first derivative of the voltage (dv/dt) on the horizontal axis The first derivative was obtained by using the *negative* channel of a differential amplifier (Tektronix Type 2A63) as a differentiating feedback am plifier Calibration of the PPC was performed as as previously described.[3]

The data was collected in several forms (1) Standard scalar ECG recordings were made on a strip chart recorder (Brush 220) as part of the clinical workup (2) Both the PPC and ECG sig nals were recorded from the oscilloscope screen with 35 mm high speed film The developed film was placed in a microfilm reader and the data were analyzed by superimposition This pro cedure was used primarily *for the* verification of the loops reconstructed by the computer (3) The amplified and filtered input voltage signal was stored on one channel of an FM tape recorder (Sangamo 3500) On a second channel of the FM tape recorder a 1 34 V rectangular pulse was synchronized with the start and stop of ECG *data* collection This signal was used as a lead change indicator in the PDP8 digital computer For com puter analysis, the recorded ECG was played into a hybrid computer system as shown in Fig 1 The ECG first entered the EAI TR20 analog com puter and the signal scaled so as to be within the range of the analog to digital (A/D) converter (± 1 1 V) The A/D converter sampled the out put of the TR20 at a rate of 4,000 samples per second These samples were converted into a 12 bit digital equivalent for processing by the PDP8 digital computer The digital signal was then stored on a digital tape Whenever a lead change was indicated by channel 2, the A/D converter was automatically turned off and the digital com puter signalled an end of group character on the digital tape When the lead change trigger re turned to threshold level the A/D converter began sampling the new lead. This process was repeated until the entire 12 leads of the patient were complete The end of patient data was indi cated by an end of file character on the digital tape Additional processing was performed on a CDC 6600 computer

An average PPC loop of 20 consecutive QRS complexes, was determined for each lead of each patient The determination of the average PPC was accomplished by introducing a one second segment of digital tape into the CDC 6600 digital computer This segment was scanned for a QRS complex, Fig 2, Step 1 The criterion used to locate the QRS complex was the maximum nega tive secant slope in excess of a threshold level The threshold level was set by the computer at 75 per cent of the maximum negative secant slope encountered in the first 3 seconds of data The relative position of the QRS complex was noted. A window 0 25 second wide and centered about the maximum negative secant point, P became the reference QRS complex as indicated in Fig 2, Step 2 The input digital signal was again read into a buffer and the point of repeatability deter mined based on the autocorrelation function and demonstrated in Fig 2, Step 3 The reference QRS complex was then averaged with this iso lated QRS complex This process Steps 3 and 4, was repeated—with appropriate *weighting fac* tors on the averaging step—*until a limiting* num ber of beats had been reached. After some ex perimentation it was determined *that 30 such complexes were sufficient*

The time of initiation and termination (points P_1 *and* P_3 *respectively*, Fig 2) of the QRS com

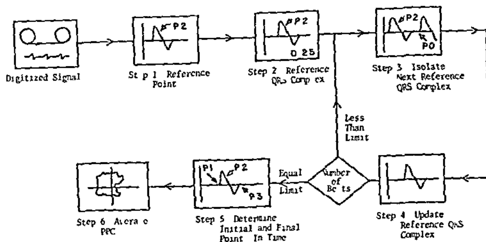


Fig 2 Analytical scheme for computer data analysis.

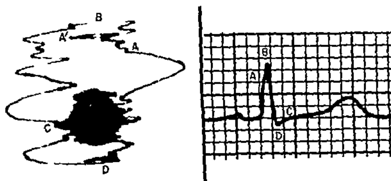


Fig 3 A, PPC loop reproduced from oscilloscope screen. B, reproduction of conventional ECG Evidence of notching and slurring can easily be seen on the PPC when the scalar ECG shows little or no change Labels *A* through *D* represent corresponding points on both the PPC and scalar ECG (see text) The central heavy black dot is produced by the P and T waves. This is due to their relatively low velocity and voltage amplitude with respect to the QRS complex. The recording was made from Lead I

plex was chosen so as to remove the high intensity of inner loops (low velocity P and T waves) evident in the photographic techniques. The derivative was determined from the least square quadratic function fitted through 5 data points and the average PPC was plotted using a Calcomp plotter The average PPC data was then saved on a digital tape for patient to patient analysis.

Results

As demonstrated from the PPC reproduced from 35 mm. film (Fig 3 *A*) evidence of notching and slurring can easily be seen on the PPC when the scalar ECG (Fig 3 *B*) shows little or no change. Beginning with the central heavy black dot (the isoelectric point) in Fig 3 *A*, the trace proceeds in a counterclockwise fashion The isoelectric point corresponds to the origin of the traditional algebraic X Y coordinates Any slurring on the scalar ECG appears as notching on the PPC and notching on the ECG appears as a secondary loop within the major PPC loop The initial trace travels upward and to the right, thus indicating vertically a positive increase in voltage and horizontally a positive increase in velocity (dv/dt) The first derivative (dv/dt) momentarily reverses direction as the voltage signal continues in a positive direction thus defining a notch (point A) This portion of the trace corresponds to the rising phase of the R wave on the standard ECG Proceeding further along the ris

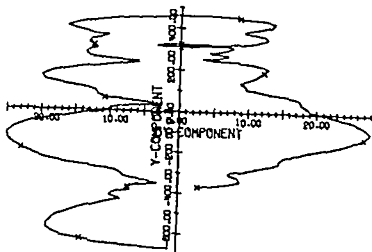


Fig 4 Reconstruction of the PPC loop by computer from data recorded on magnetic tape The similarity between details seen in the PPC loop obtained with 35 mm film (Fig 1 A) and the computer reconstruction demonstrates the high degree of resolution that can be obtained with the computer The P and T waves are not included in the computer presentation, therefore obviating the central dense region

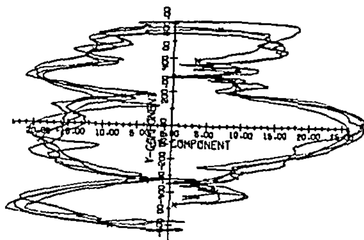


Fig 5 Superimposition of four consecutive beats from a single lead (Lead I) demonstrates the beat to beat repeatability of loop contour

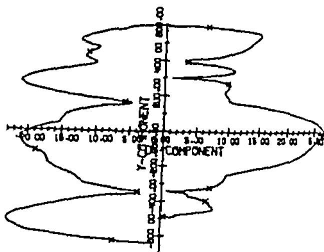


Fig 6 Computer average of 20 consecutive beats from a single lead (same subject and lead as that shown in Fig 3) The averaging procedure eliminates slight beat to beat variations without changing the major notching patterns.

ing phase of the PPC the derivative rapidly passes through zero reverses and continues in a positive voltage and velocity direction (A) This defines a secondary loop within the major PPC loop (notch in standard ECG) The first derivative then falls to zero as the trace passes directly above the isoelectric point (point B) This portion of the trace corresponds to the zenith of the R wave The trace proceeds downward and to the left producing a series of notches of different velocities The velocity of the falling phase slows as the voltage approaches the isoelectric line (point C) The trace then continues toward the maximum negative voltage where dv/dt again equals zero (point D) This corresponds to the nadir of the S wave The rising portion of the S wave is seen as a slightly notched portion of the trace which proceeds toward the isoelectric point at a relatively low velocity

It might be noted here that the P and T waves appear only in the initial dense region of the loop as a cluster of small amplitude phase plane patterns. This is due to their relatively low velocities and voltage amplitudes with respect to the QRS complex

Reconstruction of the PPC loop by computer from data recorded on magnetic tape is shown in Fig 4 The similarity between details seen in the PPC loop obtained with 35 mm film (Fig 3, A) and the computer reconstruction (Fig 4) demonstrates the high degree of resolution that can be obtained with the computer The P and T wave components are not included in the computer presentation, therefore obviating the central dense region The origin of the QRS complex in this case, starts at the zero point of the Y coordinate

Data collected from 100 male and female subjects indicated, without exception, beat to beat repeatability of loop contour within each lead of a given individual This was demonstrated both by photographic time exposures of PPC loops recorded from the oscilloscope screen and by computer analysis of 20 consecutive QRS complexes recorded on magnetic tape Superimposition of 4 consecutive beats and the average of 20 consecutive beats from a single lead (Lead I) are shown in Figs 5 and 6 respectively Examples of

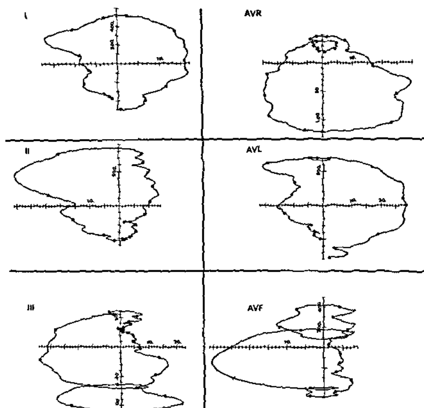


Fig 7 PPC loops for Leads I through aV_F Each loop represents the average of 20 consecutive beats from a single individual

averaged PPC loops from all 12 leads are pre sented in Figs 7 and 8

A common beat to beat variation more in loop size than in loop contour was often notable This variation is attributable to the effects of respira tion and is a phenomenon commonly observed in the standard ECG (Fig 9) By normalizing the loops to a unitary magnitude it is possible to minimize the respiration effects Thus the aver aging of 30 consecutive loops without signifi cantly affecting the notching and sublooping pat terns, is possible

PPC s were repeated on 8 subjects after inter vals ranging from 6 days to 2 5 months All cases demonstrated consistent reproducibility for the time interval studied. This observation strongly suggested that the notching patterns were of a real nature and were not due to day to day recording artifacts.

Consistency of the notching pattern has also been demonstrated to some degree on a person to person basis within 1 lead. Films of Lead V_1 from 9 female volunteer subjects were randomly selected from the age group of 18 to 24 years These were then put on an enlarger and superim posed tracings were made Two groups were noted, and a normalized loop for each was con structed by visually averaging the superimposed PPC loops (Fig 10) Each independent loop shows minor individual variations Each composite represents a general pattern of the more promi nent common notches. Group I demonstrates a voltage excursion above the isoelectric point a prominent negative dv/dt bound by 2 common notches on the falling phase and a moderately notched rising phase of relatively low positive dv/dt Group I also shows in 2 of the 5 traces a small loop at the point of maximum negative voltage Group II shows no voltage excursion above baseline a highly notched falling phase of moderate velocity and a prominent positive dv/dt excursion with 2 characteristic notches on the rising phase

Discussion

The X Y display of voltage against its corre sponding time derivative had been previously used in this laboratory and by a number of other

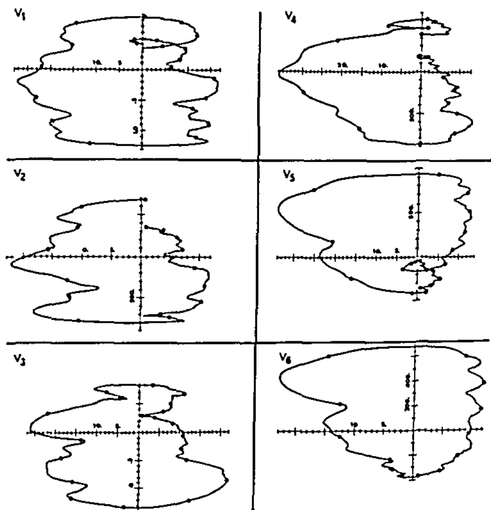


Fig 8 PPC loops for Leads V_1 through V_6 Each loop represents the average of 20 consecutive beats from the same individual as Fig 7

investigators[6 10 13] as a method for observing time dependent processes (e g , membrane potential changes and ionic conductances) in single cells Since the ECG is a time dependent process it was believed that phase plane analysis might reveal clinically significant information

Preliminary studies utilizing this technique indicated that the PPC significantly enhanced the slurring and notching patterns inherent in the QRS complex of the ECG wave form [3 4] Slurring and, to a lesser degree notching have been shown to occur in the ECG s of normal individuals [8 9 12 14] However, with an increase in the amount of pathologic myocardial involvement the amount of notching and slurring was shown to increase and thus to have diagnostic significance [2 7 8 9 11 12 14]

Evans and McRae[1] have noted that notching on the downstroke of the R wave can be a lone cardiographic finding indicating myocardial damage and cardiac infarction in a patient with chest pain ' Weinberg and co workers[14] have demonstrated that marked notching and slurring of the QRS complex was evident in 31 7 per cent of the individuals shown to have myocardial fibrosis at autopsy The authors also indicated that the notching and slurring of the QRS complex could occur normally in Lead *III* or *near the* isoelectric line in the other leads However when the notching or slurring was found near the apex of the QRS complex, in multiple leads, or in large numbers, it was considered abnormal and reflected intrinsic myocardial damage

With the use of high frequency electrocardiography (HFE) Langner and co workers[8, 9] observed that patients with myocardial infarction showed a significant increase in the incidence of high frequency notching *and slurring* as compared to normal subjects These investigators also noted that approximately 40 per cent of the subjects with angina pectoris showed an abnormal increase in high frequency notching and slurring patterns, whereas the conventional ECG indicated no significant changes In a comparative study of normal subjects and patients with myocardial disease, Reynolds and co workers[12]

also observed that the high frequency notching increased with pathologic myocardial involvement.

The PPC has the ability to enhance the slurring and notching patterns of the standard ECG. This was consistently demonstrated by the data from 100 normal subjects. In addition it was seen that repeatable notching patterns occur from beat to beat within the same subject. This, plus the fact that loop contours were consistently repeatable within subjects over a time period of at least 2½ months indicated that the notching patterns were of a physiologic origin and not due to day to day artifacts.

The PPC notching and sublooping patterns represent electrical events such as changes in the relative magnitude and direction of the mean electrical vector resulting from the complex spread of depolarization through the myocardium. According to Langner and co workers[8,9] multiple notching and slurring in the QRS complex is probably a result of a mosaic of interspersed electrically active and inert myocardial tissue. Such small areas in the normal heart could result in the notching and sublooping patterns observed in the PPC.

The ability to classify the PPC patterns of healthy individuals into groups demonstrates that the minor notching and sublooping patterns of each individual do not obscure the major loop configuration and thus allows the averaging of PPC loops from patient to patient. Such averaged population loops will permit the establishment of a reliable normal data base with which comparisons to abnormal populations can be made.

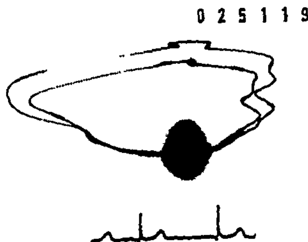


Fig 9 Photograph of two consecutive PPC loops from Lead V_6 demonstrating respiration artifact. Outer loop inspiration inner loop expiration.

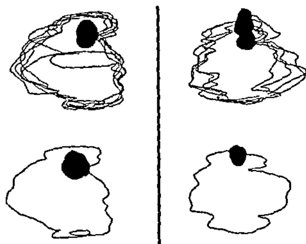


Fig 10 Top superimposed tracings of PPC loops Lead V_1 taken from 9 subjects (female ages 18 to 24 years) and divided into 2 groups. Bottom visual composites of superimposed loops, illustrating major common notching patterns.

Summary

A method for increasing the diagnostic capability of the clinical electrocardiogram has been further developed. The coordinated display of voltage against the time derivative of voltage (dv/dt) i e PPC was found to be remarkably sensitive to subtle aberrations in QRS contours not easily visualized in the standard electrocardiographic portrayal of voltage against time. A standard twelve lead electrocardiogram and phase plane loops were displayed and photographed on an oscillographic recorder the latter by placing voltage (V) on the vertical axis and the first time derivative of voltage on the horizontal axis. Data storage on magnetic tape and computer analysis of the data were also carried out. Data from 100 normal (as determined from clinical ECG history and physical examination) subjects demonstrated evident repeatable notching patterns in the PPC. The repeatability of these patterns was demonstrated from beat to beat in each lead of every individual and was found to be consistent even when the readings were taken over long periods of time. The PPC s of different individuals showed consistent common notching patterns which would indicate that anatomical and physiological bases exist to explain this phenomenon.

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Myocardial pathology after cardiac venous and lymph flow obstruction in the dog

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We have shown in acute studies that interference with venous and/or lymphatic drainage from the heart has a profound effect on myocardial function and, in chronic experiments, adversely affects healing of experimental myocardial infarctions, makes the heart valves susceptible to bacterial endocarditis, and produces ventricular endocardial fibroelastosis.[1-5] The present experiments were designed to determine the short-term and long-term effects on myocardial viability produced by cardiac venous occlusion, lymphatic occlusion, and combined venous and lymphatic occlusion.[5]

Material and methods

Sixty-six dogs were studied in which 4 types of experimental conditions were compared: (1) lymphatic obstruction, (2) venous obstruction, (3) lymphatic and venous obstruction, and (4) sham-operated control animals.

The operative techniques and postoperative care used are identical with those described previously.[6] Briefly, dogs were anesthetized with intravenous sodium pentobarbital, 30 mg. per kilogram, and were ventilated with room air by means of a Harvard respirator through a tracheal cannula. The heart was exposed through an incision in the fourth or fifth left interspace and a pericardial cradle was created by incising the parietal pericardium longitudinally.

The lymphatic channels were visualized by injecting 0.2 ml. of T-1824 dye into the myocardium. This dye is picked up preferentially by the lymphatics. After their visualization, the lymphatics were doubly ligated and severed, and the cardiac lymph nodes were resected.

The coronary sinus was ligated, as were all visible anterior veins draining the right ventricle and the great cardiac vein as it passed under the left atrial appendage. Dogs in which any impairment of the arterial circulation was produced were discarded, as were those dogs with only partial coronary sinus ligation. The animals were divided into acute and chronic experimental groups.

Acute experiments were terminated by killing the animals with an overdose of intravenous sodium pentobarbital after 1 to 24 hours of observation. In control animals, anesthesia was induced, the chest was opened, and the pericardium was incised without further intervention; approximately 4 hours later they were killed.

Dogs maintained for chronic observation were given penicillin, 1.2 million units, intramuscularly daily for 4 days. Chronic dogs that did not die spontaneously were killed with an overdose of intravenous sodium pentobarbital at different time intervals ranging from 7 to 90 days after the operative intervention. As controls for the chronic experimental animals, we used dogs that had been subjected to various procedures involving open-chest operations. They were selected randomly from available material and matched for time of observation and mode of death. The experimental procedures carried out in these control dogs consisted of narrowing of the superior vena cava and/or sectioning of the thoracic duct. A few of the dogs had barium sulfate powder instilled into the pericardial sac

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Table I Acute experiments incidence of positive HBFP staining and myocardial infarctions

Group	No. of dogs	Time (hours)		HBFP positive		Myocardial infarctions gross and microscopic	
		Mean	Range	No.	Per cent	No.	Per cent
1 Control	6	3 5	3 4	1	17	0	0
2 Lymphatic obstruction	4	3 5	2 4	3	75	0	0
3 Venous obstruction	5	5 8	3 16	5	100	0	0
4 Lymphatic and venous obstruction	5	7 0	1 24	4	80	0	0
Statistical analysis (p values)				1 vs 2	NS		
				1 vs 3	< 0 05		
				1 vs 4	NS		
				2 vs 3	NS		
				2 vs 4	NS		
				3 vs 4	NS		

NS = not significant

Table II Chronic experiments incidence of positive HBFP staining and myocardial infarctions

Group	No. of dogs	Time (days)		HBFP positive		Myocardial infarctions			
						Gross		Gross and microscopic	
		Mean	Range	No.	Per cent	No.	Per cent	No.	Per cent
1 Control	13	54	10 90	3	23	0	0	0	0
2 Lymphatic obstruction	12	45	7 90	10	83	4	33	4	33
3 Venous obstruction	6	29	14 90	3	50	2	33	2	33
4 Lymphatic and venous obstruction	15	45	13 90	14	93	6	40	13	87
Statistical analysis (p values)		1 vs 2		< 0 001		< 0 01		< 0 01	
		1 vs 3		NS		NS		NS	
		1 vs 4		< 0 001		< 0 05		< 0 001	
		2 vs 3		NS		NS		NS	
		2 vs 4		NS		NS		< 0 02	
		3 vs 4		NS		NS		NS	

NS = not significant.

Thirteen control dogs were available for comparison with the experimental dogs

Pathologic methods At autopsy the hearts were carefully dissected and the degree of occlusion or obstruction produced by the ligatures was estimated by using probes For microscopic examination, at least 2 blocks were taken from each ventricle These were obtained when possible, from the border of grossly visible abnormal areas, with inclusion of both abnormal and normal areas in the block, if no gross abnormalities were observed, standard blocks of the most commonly found abnormal regions were sampled

Tissue blocks were fixed in 10 per cent formaldehyde processed in an autotechnicon, and 5 μ thick sections were cut. These were stained routinely with hematoxylin and eosin (H & E) and resorcin Van Gieson stains We attempted to use the acid fuchsin technique to demonstrate myocardial ischemia [7] but found the results to be variable and unreliable However, we found the stain described by Lie and co workers,[8] composed of hematoxylin basic fuchsin, and picric acid (HBFP) to be reliable and satisfactory for the evaluation of myocardial ischemia

The differences between the groups of dogs



Fig 1 Left panel right ventricle coronary sinus ligation and lymphatic obstruction, 55 days postoperatively H & E original magnification, ×40 Normal appearing myocardium Right panel duplicate section, same magnification Stained with HBFP stain. Large area of positive staining fibers (dark in photograph)



Fig 2. Left panel right ventricle coronary sinus ligation, and lymphatic obstruction, 33 days postoperatively H & E original magnification, ×40 *Subendocardial fibrosis and large scar surrounding normal looking muscle bundles* Scattered calcium deposits (black in photograph) Right panel duplicate section stained with HBFP The apparently normal muscle bundles seen in the left panel are stained positively (dark) in this stain for hypoxia Calcium does not stain with HBFP neither does fibrous tissue The dark area under and parallel to the thickened endocardium is collagen *which stains positively with HBFP*

were tested for statistical significance by the chi square test

Results

The results of the acute experiments that lasted 1 to 24 hours are listed in Table I At this time ischemic areas as defined by staining with HBFP were evident in most dogs with lymphatic venous or combined lymphatic and venous occlusion. Gross or microscopic evidence of myocardial infarction was not detected.

The results of the chronic experiments are tabulated in Table II Three out of 13 or 23 per cent of the dogs in the control group (Group 1) showed HBFP positive staining areas This was a significantly lower incidence than observed in animals subjected to ligation of the lymphatic ducts (Group 2) and to the animals subjected to combined lymphatic and venous occlusion (Group 4) ($p < 0.001$) The difference between the control dogs and dogs subjected to venous occlusion alone (Group 3) was not statistically significant Although differences in HBFP staining among the three experimental groups did not reach statistical significance in any comparison a trend toward a lower incidence in the dogs with venous occlusion alone was seen

We did not observe any gross or microscopic myocardial infarctions in the control dogs of the chronic experimental group A significantly greater incidence of grossly visible myocardial infarctions was present both in the group with lymph obstruction alone ($p < 0.01$) and in the group with combined lymph and venous occlusion as compared to the control animals ($p < 0.05$) When gross and small microscopic



Fig 3 Left panel same dog as in 2 *A* and 2 *B* Left ventricle H & E, original magnification, × 40 Large fibrous and calcific scar (black in photograph) with granulation tissue and muscle bundles that show slight myocytolysis. Right panel duplicate section stained with *HBFP Scar (in the right upper corner)* not stained (light) Some positive (black) staining fibers within the scar around the capillaries large areas of positive (black) and negative (light) staining muscle bundles in close proximity

infarctions combined were evaluated a statistically significant difference was observed both between the control dogs and the dogs with *lymph obstruction* ($p < 0.01$) and the control dogs and the dogs with combined lymph and venous obstruction ($p < 0.001$) Here too, a significantly *greater amount* of abnormalities was present in the dogs with combined obstruction of lymph and venous channels than in the animals with lymphatic obstruction alone ($p < 0.02$) Thus, lymphatic occlusion alone and venous occlusion alone led to some large grossly visible myocardial infarctions, but combined compromise of both the venous and lymph outflow led to a significant additional occurrence of numerous small microscopic infarctions Figs 1 through 3 illustrate typical findings obtained in H & E and HBFP stained sections

It is of interest to note that in those dogs that developed demonstrable lesions these lesions generally were observed in both the right and left ventricle

Discussion

McAllister and Leighninger[9] reported right ventricular myocardial infarctions resulting from coronary sinus and anterior coronary vein ligation They pointed out that the superficial venous drainage has to be completely occluded, including all the anterior coronary veins that drain directly into the right atrium in order to produce right ventricular infarction Lymph duct ligation was not carried out in their experiments From our data in chronic animals presented here, it can be seen that the occurrence of myocardial damage is significantly increased if total venous and lymphatic obstruction is compared to lymphatic obstruction alone Because of the relatively small number of dogs subjected to venous occlusion alone, the difference between a single and combined procedure does not reach statistical significance, although the trend is highly suggestive of an increased effect of the combined procedure The observation of myocardial infarction in the long term experiments is in accord with the findings of HBFP positivity indicative of ischemia seen in the acute (<24 hours) experiments (Table I) Lie and co workers[8] who developed this stain observed in dogs and man the progression from ischemic muscle staining with HBFP to necrosis of muscle bundles not stained to the final development of myocardial fibrosis and scar formation which also does not take this particular basic fuchsin stain These last stages can be readily seen in our material The potential importance in humans of abnormalities in venous drainage has been emphasized recently by Datta and Gupta[11] who concluded from autopsy studies that obstruction to the venous outflow from the heart may contribute to congestive heart failure and left ventricular hypertrophy

The long term persistence of the HBFP stainability without progression noted in the majority of the chronic experimental animals remains unexplained. Lie and co workers[8] considered the changes to be specific for ischemia occurring after arterial occlusion, which they

looked on as the first stage in myocardial infarction They postulated that the stain is taken up by a labile protein that is produced as a result of the ischemic process The exact nature of the substance stained in this manner however is not yet known It is possible that in our experimental model interference with protein metabolism or deposition of a labile protein may have occurred. Why such fibers did not become completely necrotic is unknown It will be necessary to study myocardium that is chronically ischemic or hypoxic due to different disease mechanisms (e g in congenital heart disease or in chronic pulmonary disease) to determine whether it is possible for muscle fibers to remain viable after having been damaged to the extent that they react positively with basic fuchsin dyes Another hypothetical explanation is that viable fibers located within an area of infarction become progressively ischemic over a long period of time

In these and other experiments in our own laboratory we have determined that in our hands myocardial fibers have to be anoxic for at least 1 hour to be stained positively with HBFP Thus a fairly advanced degree of cellular damage has to occur before the abnormal staining becomes demonstrable The process of anesthetization and death employed in this study therefore could not have accounted for the changes since it was carried out in less than 10 minutes The question remains as to the significance and meaning of HBFP positive staining of fibers surrounding a well developed and obviously old (up to 90 days after operation) scar This finding suggests however that areas of potentially reversible hypoxia and resultant myocardial dysfunction can exist chronically in the heart and provides a further theoretical and experimental basis for myocardial revascularization procedures

Summary

This study carried out in dogs was designed to elucidate the effects of cardiac lymphatic and venous obstruction both separate and combined, on the viability of the myocardium Specimens were stained with HBFP to demonstrate ischemia Eleven dogs had venous obstruction 5 dogs were acute (killed within 24 hours) and 6 dogs were chronic. Sixteen dogs had lymph obstruction, 4 dogs were acute and 12 dogs were chronic Twenty dogs had lymph obstruction in addition to venous obstruction 5 dogs were acute and 15 dogs were chronic Nineteen animals served as control animals 6 dogs were acute and 13 dogs were chronic Autopsies excluded all animals with any compromise of the arterial circulation Large areas of myocardial fibers staining positively with HBFP were seen in acute and chronic experimental dogs from 1 hour to 90 days after operation No gross or microscopic infarctions were found in the acute or chronic control dogs Thirty three per cent of dogs with chronic venous obstruction or chronic lymph obstruction showed gross infarctions without additional microscopic areas of infarction In dogs with combined venous and lymphatic obstruction 40 per cent had gross infarctions whereas 87 per cent had a combination of gross plus microscopically evident infarctions Thus interference with the outflow of venous blood and lymph without interference with the arterial blood supply can lead to significant myocardial pathology of a type usually associated with a deficit in arterial blood supply If as has been postulated the HBFP stain is specific for ischemic muscle fibers, our results seem to indicate that such a stage of ischemia can persist over a prolonged period of time without progressing to necrosis or alternatively that over the course of time progressively more fibers that are in or near a fibrotic area slowly become ischemic These findings in dogs provide support for the potential usefulness of myocardial revascularization procedures

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Manifestation of the Wolff Parkinson-White syndrome after myocardial infarction

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The Wolff Parkinson White (WPW) or pre excitation syndrome is characterized by the electrocardiographic evidence of an abnormally short PR interval with a prolonged QRS containing a delta wave in the presence of a sinus rhythm[1] and is seen either in this classical form[1] or in its variant forms[2,3] Besides the more common congenital variety both experimental[4] and acquired[5] forms have also been described. The recognition of this abnormality is important not only because of its association with paroxysmal tachyarrhythmias in otherwise healthy individuals but also as it may mimic the ECG pattern of myocardial ischemia by producing abnormal ventricular repolarization In addition it is also difficult to make the diagnosis of acute transmural myocardial infarction in the presence of WPW syndrome as in its presence the initial positivity within the ventricular cavity does not permit the development of QS deflection[6] It is evident by the facts that so far only a few cases of WPW syndrome with unequivocal ECG diagnosis of myocardial infarction have been reported in the literature[7,8] Reports on the appearance of the WPW syndrome after acute myocardial infarction are notably sparse We have recently encountered two patients with this rare association within a week and they are the subject of this communication

Case reports

Case 1 Mr B J a 75 year old white man was hospitalized for leaking abdominal aneurysm. The patient had a long history of scoliosis osteoporosis and back pain of several years duration. Eight days prior to admission, he noted a low grade abdominal distress An x ray film of the abdomen revealed an abdominal aneurysm In addition to this, the patient had a long history of ischemic heart disease manifested by angina pectoris and exertional dyspnea for which he was treated with Isordil and digoxin A history of occasional palpitation for many years was also obtained. Many ECGs had been obtained from the patient on numerous occasions for about 15 years prior to the hospitalization. The review of these ECGs showed supraventricular tachycardia on two occasions but no evidence of the WPW syndrome On the third day of his hospitalization he developed severe chest pain and an ECG taken on the same day showed inferior wall myocardial infarction (Fig 1*A*) He had several attacks of paroxysmal supraventricular tachycardia for the next two days (Fig 1*B*) and a subsequent ECG showed sinus rhythm and the pre excitation pattern (Fig 1*C*) The ECG pattern of myocardial infarction was completely masked. The patient had surgery for the aneurysm after an uneventful course of myocardial infarction, and a follow up ECG taken three months after his discharge showed evidence of old inferior wall infarction but no WPW syndrome

Case 2 Mr F N a 59 year-old white man with a long history of manic depressive psychosis, was admitted to the psychiatry service and he developed a cardiac arrest during electric shock therapy on the day of admission A previous history of occasional anterior chest pain for many years and recent episodes of palpitation was obtained from the family The review of several ECGs obtained from the patient for two years prior to the admission failed to demonstrate the WPW syndrome The post resuscitation ECG was consistent with an acute anteroseptal myocardial infarction (Fig 2*A*) Serum glutamic oxaloacetic transaminase lactic dehydrogenase, and creatine phosphokinase activity were markedly elevated During the first few hours, he had several brief bursts of supraventricular tachycardia (Fig 2*B*) and recurrence of the tachycardia was later prevented after the institution of quinidine therapy A week later he complained of palpitation and an ECG taken at that time again showed supraventricular tachycardia and anterior wall myocardial infarction. The tachycardia responded to carotid sinus massage and a follow up ECG (Fig 2*C*) on the same day uncovered the WPW syndrome with a normal sinus rate of 80 per minute The pattern of anterior wall infarction disappeared completely from his ECGs He had an uneventful course of myocardial infarction and was discharged, and a subsequent

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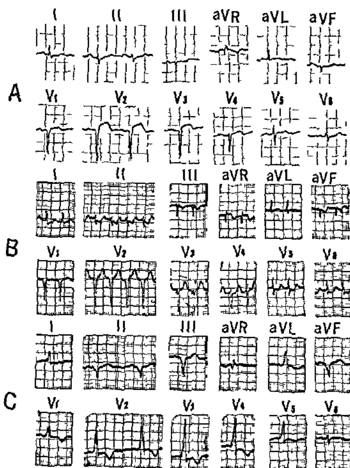


Fig 2 A through C Electrocardiograms of Case 2 See text for description

enhanced conduction in the previously blocked aberrant bundle The underlying anatomic feature of the WPW syndrome is considered to be the bundle of Kent which consists of ordinary muscle fibers[12] Acetylcholine improves conductivity of the atrial muscle tissue by increasing the membrane responsiveness[11] and catecholamines increase excitability and conductivity of the ventricular muscle[13] If the Kent bundle is like ordinary atrial or ventricular muscle and responsive to acetylcholine or catecholamines then the WPW pattern could be elicited by increased cholinergic or adrenergic discharge Increased autonomic nervous activity is a significant feature of the response to acute myocardial infarction Therefore it is possible that conduction in the aberrant bundle was improved by increased humoral influences in our patients during myocardial infarction resulting in successful propagation through the aberrant bundle and the appearance of WPW syndrome In both patients, the WPW pattern disappeared after the recovery from acute myocardial infarction

Summary

Two cases of the WPW syndrome appearing after the development of myocardial infarction are reported. The pattern of myocardial infarction disappeared completely with the appearance of the preexcitation pattern on the patients ECGs. It is assumed that an aberrant bundle became functional under the influence of increased autonomic nervous activity accompanying acute myocardial infarction The aberrant bundle probably failed to propagate in the A V direction prior to the development of myocardial infarction but it occasionally succeeded in propagating in the V A direction to form a circus movement loop with the A V node The occasional establishment of such circus movement

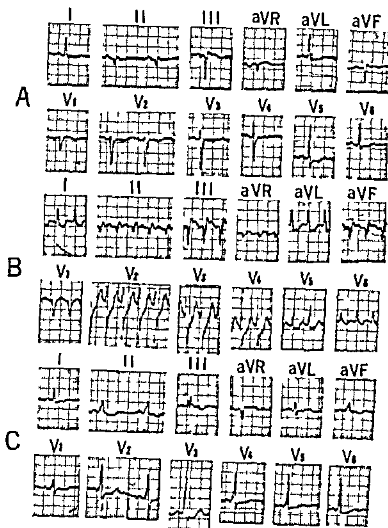


Fig 1 A through C Electrocardiograms of Case 1 See text for description

ECG taken six months after his discharge showed no evidence of the WPW syndrome

Discussion

Both patients reported here are examples of the so called acquired variety of WPW syndrome with the ventricular pre excitation pattern appearing after myocardial infarction Levine and Burge[9] reported a case of acute myocardial infarction with an advanced degree of A V block, in which occasionally conducted beats had the characteristics of WPW syndrome This and all other previously reported cases of the acquired WPW syndrome were associated with severe arteriosclerotic heart disease,[5] myocardial infarction, or disease of the A V node [9] There can be several possible mechanisms for the appearance of the WPW syndrome following acute myocardial infarction, and one could be the presence of an accessory bundle which overtakes conduction from the normal A V conduction system In the case of Levine and Burge,[9] an accessory bundle was indeed found on autopsy One may speculate that the presence of an accessory connection may be life saving in some patients who develop a block in the normal A V conduction system. The difficulty one faces in making the ECG diagnosis of myocardial infarction in the presence of WPW syndrome is well recognized [7,8] This difficulty arises because the syndrome may mask the ECG changes of myocardial infarction, since the initial positivity within the ventricular cavity does not permit the development of QS deflection even in the presence of transmural infarction [4] In both of our patients, the pattern of myocardial infarction indeed disappeared when the WPW pattern was manifested on their ECGs.

Both of our patients had episodes of palpitation consistent with paroxysmal supraventricular tachycardia prior to the development of myocardial infarction In one of the patients, episodes of supraventricular tachycardia had been documented on earlier ECGs. It is possible that these episodes of tachyarrhythmia may have been due to an aberrant A V connection that never propagated in the A V direction and were therefore never exposed on routine ECGs. However, such an aberrant pathway may occasionally succeed in propagating in the V A direction to initiate supraventricular tachycardia Recent evidence has firmly established the underlying mechanism of supraventricular tachycardia to be due to a circus movement involving the orthograde conduction through the A V node and the retrograde conduction through an aberrant bundle [10] The narrow QRS complexes observed during episodes of supraventricular tachycardia in both of our patients indicate that the re entrant impulses depolarized the ventricles through the normal A V conduction system and returned to the atria over the aberrant pathway

If an aberrant bundle is a narrow isthmus of muscle tissue connecting the atrial tissue with the ventricular muscle the margin of safety for successful propagation may be low and a conduction block may occur at the isthmus. A recent study demonstrated that unidirectional block can occur at the junction of the narrow band with the larger areas of the atrial tissue and the block can be relieved by acetylcholine [11] The sudden appearance of the WPW syndrome in our patients during myocardial infarction suggests

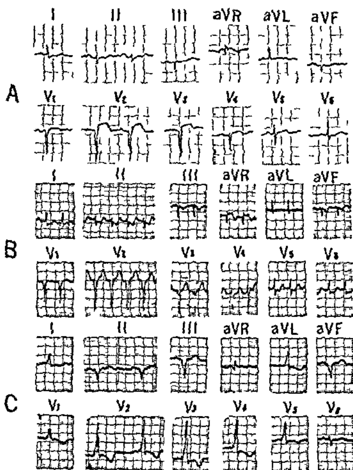


Fig 2 A through C Electrocardiograms of Case 2 See text for description.

enhanced conduction in the previously blocked aberrant bundle The underlying anatomic feature of the WPW syndrome is considered to be the bundle of Kent which consists of ordinary muscle fibers[12] Acetylcholine improves conductivity of the atrial muscle tissue by increasing the membrane responsiveness[11] and catecholamines increase excitability and conductivity of the ventricular muscle[13] If the Kent bundle is like ordinary atrial or ventricular muscle and responsive to acetylcholine or catecholamines, then the WPW pattern could be elicited by increased cholinergic or adrenergic discharge Increased autonomic nervous activity is a significant feature of the response to acute myocardial infarction Therefore it is possible that conduction in the aberrant bundle was improved by increased humoral influences in our patients during myocardial infarction resulting in successful propagation through the aberrant bundle and the appearance of WPW syndrome In both patients the WPW pattern disappeared after the recovery from acute myocardial infarction

Summary

Two cases of the WPW syndrome appearing after the development of myocardial infarction are reported. The pattern of myocardial infarction disappeared completely with the appearance of the preexcitation pattern on the patients ECGs It is assumed that an aberrant bundle became functional under the influence of increased autonomic nervous activity accompanying acute myocardial infarction The aberrant bundle probably failed to propagate in the A V direction prior to the development of myocardial infarction but it occasionally succeeded in propagating in the V A direction to form a circus movement loop with the A V node The occasional establishment of such circus movement

may have been responsible for the episodes of supraventricular tachycardia in these two patients

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Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus

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Cardiac involvement of various types in systemic lupus erythematosus (SLE) is common, all layers being susceptible to involvement Coronary arterial manifestations are less common and, when present, usually take the form of a vasculitis of the small branches Disease of the large coronary arteries has been reported only rarely When present these usually are of inflammatory nature *SLE is not generally considered a predisposing cause of atherosclerosis*

Nevertheless we observed a 29 year old woman with SLE who died of myocardial infarction secondary to severe atherosclerotic changes in the coronary arteries As none of the commonly recognized causes of coronary atherosclerosis in young women were present, we are prompted to place this case on record

Case report

Clinical features The patient, a Caucasian woman died at age 29 years. From the age of 16 years, she had suffered from repeated episodes of painful joints pleurisy and pericarditis. While pregnant at age 20 years, she developed features of the nephrotic syndrome and thrombocytopenia Following cesarean section at term, her condition improved. Other features of note during this period were the development of a blotchy facial rash in butterfly distribution and a nasoseptal perforation The diagnosis of lupus erythematosus was confirmed by positive antinuclear antibody estimation with dinitrophenol 1 16 desoxyribose nucleic acid 1 8 and a positive bead fibrogen lupus erythematosus clot test.

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Steroid treatment was initiated (prednisone 30 mg per day) Blood pressure was normal until that time (120/70 mm. Hg) *The family history was negative for atherosclerotic* heart disease Levels of serum cholesterol and triglycerides were within normal limits There was no history or evidence of diabetes or hypothyroidism With steroid treatment the patient s condition improved *For the next five years her* course was relatively benign. She was then readmitted to the University of Minnesota Hospitals because of loss of hair poor appetite sun sensitivity and an erythematous maculopapular pruritic rash over the extensor surface of both arms face upper chest, and neck. Of note on that admission were a blood pressure of 150/90 mm. Hg and mild pedal edema. The liver was palpable 1 5 cm below the right costal margin. The electrocardiogram, at the age of 27 years revealed abnormalities interpreted as probable old diaphragmatic myocardial infarction and nonspecific ST T wave changes The patient s condition improved although she still *complained of fatigue and dyspnea.*

In November 1971 at the age of 29 years the patient was admitted to the coronary care unit of the University of Minnesota Hospitals because of substernal thoracic pain which radiated to the back and both shoulders *Between admissions* the blood pressure had been erratically controlled and, at the time of admission she was receiving Aldomet 500 mg three times a day in addition to prednisone 25 mg. every other day Aldactone 25 mg three times a day and chloroquine 250 mg daily

Upon physical examination, of note were the blood pressure reading of 110/80 mm Hg a hyperdynamic left ventricle and a Grade II/VI holosystolic murmur maximal at the apex the murmur radiated to the left axilla

The electrocardiogram revealed signs of an evolving inferior myocardial infarction (Fig 1) She subsequently developed ventricular tachycardia and died one day after admission

Pathologic findings The significant positive autopsy findings were in the heart, coronary arteries, and brain.

The heart, including the pericardium which was adherent to the heart, weighed 400 grams. In general the mitral leaflets were delicate and the chordae and commissures were normal The anterior mitral leaflet showed a focus of brownish discoloration measuring about 1 5 cm. in diameter On the atrial aspect of the center of this area was a small,

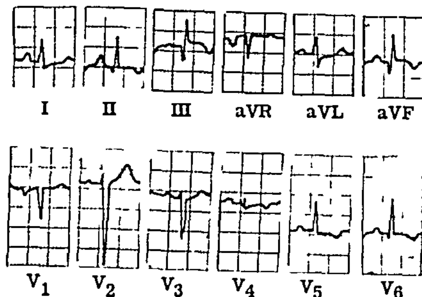


Fig 1 Electrocardiogram taken during the last admission.



Fig 2 A and B *A* The mitral valve The leaflets show mild thickening at the line of closure At the base of the anterior mitral leaflet is a localized lesion *(between arrows)* of which the histologic section is illustrated in *B*. *B*, Section through mitral valve through the discolored lesion shown in *A* The process is represented by a vegetation, the base of which is formed by fibrous tissue (Hematoxylin and eosin Original magnification ×75)

friable flat vegetation measuring about 4 mm in diameter and about 2 mm in height (Fig 2*A*) Histologically this consisted of organizing vegetative material deposited upon the atrial aspect of the leaflet The latter showed slight fibrous thickening (Fig 2*B*)

A healed infarct overlain by a mural thrombus was present at the apex of the left ventricle There was also evidence of an acute posteroseptal myocardial infarct Histologically this area was characterized by necrosis of myocardial fibers and by heavy leukocytic infiltration (Fig 3)

In many foci the major coronary arterial trunks showed marked atherosclerotic changes with narrowing of the lumen up to 90 per cent of their original calibers Two cm from its origin the right coronary artery showed complete occlusion of its lumen by a recent thrombus (Fig 4*A*) Also the right coronary artery in the segment between the origins of its marginal and posterior descending branches was occluded by an organized thrombus

Histologically the coronary arterial lesions were characteristic of atherosclerosis *No signs of arteritis* either active or healed were encountered (Fig 4*B* and *C*) The adventitial lymphocytic infiltration present was considered within the range of change classically associated with coronary atherosclerosis.

The aorta, the renal arteries and the arteries at the base of the brain showed marked atherosclerotic changes Small foci of healed cerebral infarction each measuring less than 1 cm in diameter were located in the white matter of the right middle frontal gyrus the right occipital lobe and the right caudate nucleus

Except for small scars considered of vascular origin the kidneys showed the most significant changes upon histologic examination. These took the form of glomerular changes which were characterized by some hypercellularity and prominent highly refractile basement membranes yielding the wire loop" change of lupus erythematosus (Fig 5A) The spleen which was not remarkable upon gross examination histologically showed onion peel" proliferation of fibroblasts around the arteries a change which also was supportive of the diagnosis of lupus erythematosus (Fig 5B)

Comment

The cause of death in SLE is usually related to renal insufficiency and infection although very rarely myocardial infarction has been reported as a major complication In the latter regard Shearn[1] stated that there was no proof for the pathologic changes associated with the lupus process to have ever resulted in occlusion of a major coronary artery While citing several works in which coronary atherosclerosis was found in patients dying of lupus erythematosus, he expressed the general view that there was no relationship between these two conditions.

While the literature on the subject of myocardial infarction in association with SLE has certain confusing elements certain features are clear In some cases there is pathologic proof of arteritis as the basis for myocardial infarction [2,3] while in others classical atherosclerosis has been demonstrated pathologically to be the cause of the myocardial infarction [4,5]

Sclerotic lesions of coronary arteries may be variously interpreted as to their fundamental nature Rich and Gregory[6] demonstrated that sclerotic lesions of the coronary arteries of the type seen in rheumatic fever periarteritis nodosa and experimental serum sickness may occur in patients with lupus erythematosus. These lesions may include intimal proliferation leading to narrowing of the involved vessels. Since they occur in children it was suggested that the lesions were related to the lupus process rather than to primary coronary disease

While one may recognize a misinterpretation as to the nature of arterial lesions, there are some cases in which the coronary lesions are typically atherosclerotic in nature Such lesions



Fig 3 Photomicrograph of diaphragmatic wall of the left ventricle showing features of acute myocardial infarction associated with heavy leukocytic interstitial infiltration. (Hematoxylin and eosin Original magnification × 150)

were present in our case as well as in those of Kong and associates[5] The latter authors in a review of 30 cases of lupus erythematosus reported two cases with myocardial infarction one a 42 year old white woman and one a 46 year old white man In both cases myocardial infarction was secondary to coronary atherosclerosis. No evidence of other predisposing causes of the arterial lesions was presented for these cases.

Hejtmancik and associates[4] reported coronary arterial disease in seven of 162 patients with SLE The one patient who was studied at autopsy was a mildly hypertensive 42 year old man whose death resulted from myocardial infarction Histologic examination showed arteritis of the small coronary branches but coronary atherosclerosis with acute occlusion was also found.

There remains the unsettled question as to whether there is a coincidental association or whether some factor of SLE has an atherogenic tendency Among these is to be included healed arteritis but no evidence for this association is clearly established nor was it identified in our case One cannot exclude some occult phenomenon in SLE such as an autoimmune reaction

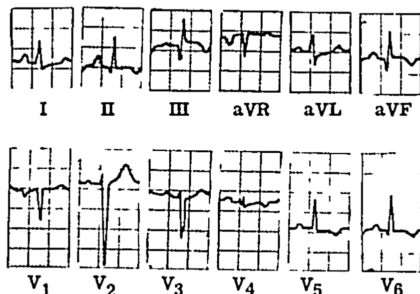


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which might predispose the arteries to atherosclerosis

Recognizing that coronary atherosclerosis may be associated with SLE in young persons one is not justified in explaining this process in dealing *with acute myocardial* infarction among patients with SLE unless there is a pathologic basis for so doing

Summary

In a 29 year old woman with systemic lupus erythematosus death was the result of acute myocardial infarction associated with extensive coronary atherosclerosis The first of two myocardial infarcts was identified at 27 years of age

None of the recognized underlying factors for premature *atherosclerosis was identified.*

An association between lupus and atherosclerosis has previously been reported in a limited number of cases

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Fig 4 A through C Representative sections of coronary arteries showing atherosclerosis *A*, The markedly narrowed lumen of the proximal portion of the right coronary artery is occluded by a recent thrombus (Elastic tissue stain Original magnification × 10) *B* Elastic tissue stain Original magnification × 10 *C*, Elastic tissue stain. Original magnification × 13 4



Fig 5 A and B *A* Photomicrograph of renal glomerulus Prominent refractile basement membrane as well as moderate increase in cellularity (Hematoxylin and eosin. Original magnification × *400*) *B* A splenic artery shows adventitial onion peel proliferation (Hematoxylin and eosin Original magnification × 100)

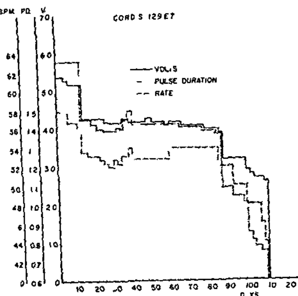


Fig 1A. Typical explantation changes in interval amplitude, and voltage (shaded area) of Cordis 129E (see text)

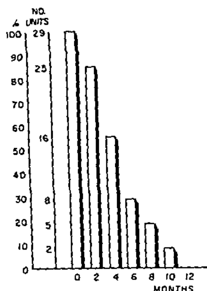


Fig 1B Explantation bar graph Pulse generators (Cordis 129E) kept in body temperature saline until complete failure

Basic concepts

Every surveillance system is based upon an analysis of one or more characteristics of the pulse generator electrical output[5,8] A pulse generator produces an electrical impulse that is generally rectangular or trapezoidal in shape With each electrical impulse the pulse generator may also produce a small radio frequency emission that can be detected by an appropriate receiver When the waveform is suitably amplified and displayed it may then be analyzed with respect to amplitude duration shape and rate of repetition (Fig 2) Other functions of the pacemaker are also measurable In noncompetitive pacemakers these include the sensitivity of the sensing circuit and the duration of the absolute and relative refractory periods.

The configuration of the electrical impulse is also influenced by factors other than battery voltage such as changes in behavior of electrical components in the circuit, the electrical impedance of the body tissues and electrode and body temperature (Table I) The integrity of the entire pacemaker system must of course be judged by whether or not the heart responds to the pacemaker stimulus. A noncompetitive pacemaker must also respond to the electrocardiographic (ECG) complex it is designed to sense but not to other complexes or extraneous electrical impulses.

In selecting a pacemaker surveillance system the above parameters may all be evaluated but some are more important than others[5] The most important ones are (1) response of the heart to the pacemaker impulse (2) rate (interval) of pacemaker (3) amplitude of pacing artifact (4) pulse duration (5) integrity of the sensing circuit

Misdiagnosis of pacemaker failure

If a pacemaker is replaced too early the only unpleasant consequences are the attendant emotional and financial expense and the danger of operative complications Errors in the other extreme namely replacement *after* pacemaker failure has occurred, carry with them the dangers of sudden death and/or the psychological, physical and financial strain of an emergency operation Analysis of the 234 deaths in our series of patients in the past 12 years showed that only one was directly attributable to cessation of pacemaker function (0 4 per cent of the deaths) Looked at in a more *unfavorable* way there were 40 instances of sudden complete failure of the pacemaker and one of these patients died (2 5 per cent) It is therefore clear that the danger of sudden pacing failure is small but

This is not to say that there were no other types of pacemaker related deaths. There were actually 16 of these including two from runaway rates, six postoperative, and eight sudden that were thought to be caused by competition.[9]

Follow-up of implanted pacemakers

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Eighty per cent of implanted pacemakers fail because of battery exhaustion One reason for establishing a pacemaker follow up system is to enable the treating physician to detect *in advance* signs that might indicate that the batteries are reaching the end of their life In a recent survey of pacemaker centers in the United States and Canada 52 per cent of the respondents considered a pacemaker clinic to be the follow up method of choice and 90 per cent used one system or another to provide postoperative service [1] Unfortunately all patients do not receive satisfactory care A study of pacemaker patients coming to autopsy in Los Angeles revealed that almost half had had no follow up instructions whatever [2]

In the past few years many methods of surveillance of implanted pacemakers have been developed and anyone who is interested in this problem may find himself hard pressed to choose the best one Techniques vary from simple office procedures to rather elaborate computerized in hospital pacemaker clinics In order to select from these one must know what aspects of pacemaker function can be measured quantitatively, what the signs and modes of pacemaker failure are, and what constitutes an adequate warning that failure is imminent One should also know the consequences of premature or late pacemaker replacement with respect to the patient s safety and life and one must be familiar with the relative advantages of each surveillance system with regard to convenience, efficiency, and expense Definite answers to these questions are not available because a satisfactory surveillance system for one clinical group may be quite unsatisfactory for another depending upon locale, available facilities, type of medical practice, and model of pacemaker in general use

Prediction of battery failure is based upon the known performance of the mercury zinc silver cell which, until the present time has been the battery used in almost all available pacemakers. This cell maintains constant voltage until some point near the end of life, at which time battery voltage drops rapidly below the level required to operate the electronic circuit of the pulse generator The rate of fall in voltage depends upon the current drain and the ambient temperature In studying the end of life behavior of a number of pacemaker models we have demonstrated that once a drop in battery voltage occurs complete failure of the pulse generator will follow in somewhere between 15 days and 10 months [3] Actually pacemakers tend to behave somewhat differently depending upon the model Important information has been gained by analyzing the performance of the explanted pulse generator in body temperature saline with the pacemaker under a nominal resistive load (Figs 1*A* and 1*B*) Similar information has been reported by others [4] A knowledge of battery exhaustion *of every model of pacemaker* is needed in order to form a reasonably accurate judgment on the timing of pacemaker replacement

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Table I Variables of pacemaker function that can be measured and that might be useful in a pacemaker follow up system also factors that may influence pacemaker performance

Parameters of pacemaker performance that are measurable
- Waveform
  - Amplitude at various points
  - Duration
  - Wave shape
  - Repetition rate (with and without magnet)
  - Refractory period
    - Duration
    - Sensitivity
- Pacing response
  - Stimulation of heart
  - Sensing of R wave
- Special functions
  - Bifocal—A V delay (American Optical)
  - Configuration of tracking pulse (Starr Edwards)
  - Direct measurements from electrodes (Medcor)
  - Programmability (Cordis and Medtronic)
  - Threshold determination (Cordis, Medtronic Medcor)

Factors that affect pacemaker performance
- Battery voltage
- Body position during tests
- Component changes
- Impedance changes
  - Frayed wire
  - Scarring at electrodes
- Intermittent electrode contact
- Biologic
  - Body temperature
  - Position
  - Time of day
  - Electrolyte imbalance
  - Effects of competing rhythms
  - Drugs
  - Sleep

An interesting alternate technique has been suggested in which a stopwatch read to a fraction of a second is used to determine the time required for 100 beats to occur [12] This method may also be employed over the telephone with the patient holding a portable transistor radio tuned to a low frequency over the pacemaker itself The radio frequency click can be counted remotely in the doctor s office. It must be remembered that this technique and others like it, are limited to

Table II List of all reasons for pacemaker replacement (exclusive of first seven postoperative days) in 1971 72*

Reason	No	Per cent
Battery failure	155 (4)	63
Patient or M D choice	34	14
Wire fracture	12 (10)	5
High threshold	9 (6)	4
Extrusion	9	4
Component failure	8 (6)	3
Rate out of specs	7	3
Electrode malposition	4 (1)	2
Inadequate R wave	2	1
Broken pin	2 (1)	1
Broken insulation	1	
Runaway rate	1 (1)	
Missing plug	1	
	245 (29)	

*Elective replacement, 88 per cent.

Table III Pulse generator replacement for battery exhaustion in the past four years

	1969	1970	1971	1972
Battery	82 (84%)	97 (86%)	70 (76%)	85 (79%)
Components leads connectors	16	16	22	22
Total	98	113	92	107

fixed rate pacemakers and to noncompetitive units operating in their free running rate This method is a modification of radiofrequency auscultation described by Furman and Escher [13]

Simple office examination will provide satisfactory doctor patient relationships but except under unusual circumstances fails to provide opportunities for in depth analysis of pacemaker problems Taking the pacemaker rate manually or from an ECG is not accurate enough to demonstrate early and subtle changes of pacemaker performance One might add phone monitoring to this system but at that point the office procedure becomes in fact more like a pacemaker clinic, the attributes of which will be discussed.

Transtelephone monitoring Over the telephone it is possible to measure impulse interval

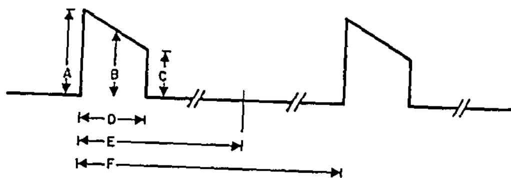


Fig 2 Diagram of typical pacemaker electrical pulse

nevertheless not insignificant. This eventuality is not as dangerous as it might appear because 86 per cent of patients will revert to some sort of spontaneous rhythm usually the *status quo ante* Thus very few patients are completely pacemaker dependent in the sense that sudden failure to pace will result in asystole for a period sufficiently long to produce irreversible cerebral or cardiovascular damage

Analysis of reasons for pacemaker replacement over the last two years is illustrated in Table II If one excludes all elective procedures (Table III) and analyzes just the replacements related to pacemaker failure approximately 81 per cent were for battery exhaustion Thus detection of impending battery exhaustion will suffice in a great majority of pacemaker replacements One out of five failures however, is due to other causes such as broken wire insulation high threshold, electrode dislodgement, or random component defects that produce alteration in pacemaker rate or output configuration Half of these may also be detected (see below) so that about 90 per cent of all problems may be diagnosed by an adequate surveillance system

Surveillance methods

Replacement at a specified time Before discussing surveillance methods a mention must be made of *no* surveillance One exteme is to do nothing at all and remove the pacemaker after it has failed This has been recommended by some, practiced inadvertently by others and was actually the rule before 1966 when the first clinics were established Although it is not a dangerous technique, emergency replacement of pacemakers usually requires two operations immediate placement of a temporary transvenous pacing system and then the actual replacement of the permanent unit This experience was so unpleasant to both doctor and patient that it actually led to the development of surveillance clinics

Another alternative is to replace the pacemaker at a date selected by the manufacturer based upon his estimate of battery life A brief glance at the past will attest to the failure of this method because prediction of battery life was notoriously wrong, with original estimates of five years compared to something less than two years in actual experience If one were to replace pacemakers at an opportune time, such as 24 months or even 30 or 36 months as is now suggested by some manufacturers for some models, there would be an important number of failures that were 'premature depending upon the make of the pacemaker, and there would also be many pacemakers removed much too soon An example of this can be seen in Fig 3 Pacemaker replacement was suggested at 18 to 20 months for Cordis 129E but more than half lasted longer than 24 months and a few longer than 30 Manufacturers will continue to recommend arbitrary replacement dates for those users who choose to follow this method.

In attempting to determine what method of pacemaker surveillance is appropriate for a given set of circumstances it might be best to establish a minimum set of criteria for a follow up system to examine how each system would fulfill these requirements (1) maintenance of good doctor patient relationship, (2) accuracy and reliability of method (3) immediate availability of test results (4) opportunity for clinical review of both patient and pacemaker (5) opportunity for physician team to maintain clinical expertise

Office procedures It is common practice for the treating physician to see patients at routine intervals in his office to take standard ECG rhythm strips and to examine the patient The pulse rate is counted accurately for a period of a minute or more and compared to previous results

Table IV List of reasons for pacemaker replace ment (1971 1972) related only to specific compo *nents of the pacing system* based on findings detected by waveform analysis

Reason for replacement	*No.*	*Per cent of total*	*No detected*	*Per cent detected*	
Battery exhaustion	155	76 7	151	97	
Wire fracture	12	5 9	2	17	
High threshold	9	4 5	3	33	
Component	8	3 9	2	25	
Rate out of specs	7	3 5	7	100	
Electrode malposition	4	1 9	3	75	46 8%
Impulse sensing (low signal)	2	1	2		
Broken pin	2	1	1		
Broken insulation	1	0 5	1		
Runaway	1	0 5	0		
Missing plug	1	0 5	1		
	202		173	85 6	

monitoring of the rate and in some instances of the ECG is added. Telephone monitoring is used as the *only* means of follow up if for some reason the patient cannot attend the clinic

During a clinic visit the patient is interviewed and examined briefly an ECG rhythm strip is taken and waveform analysis is performed. This includes evaluation of the output pulse with regard to its rate (interval) amplitude duration and configuration (see Fig 2) The information thus *obtained* is inserted into a computer that produces an updated report comparing the pre sent evaluation with all previous evaluations of that pacemaker Such record keeping makes assessment of pacemaker performance ex tremely efficient and accurate

Results of clinic method

The reasons that pacemakers were replaced at the Newark Beth Israel Medical Center are listed in Table II As can be seen there are many reasons to replace a pacemaker *other than* bat tery exhaustion Eighteen per cent of replace ments were either elective based upon the choice of the physician or the patient, or related to surgical problems such as extrusion of the pace maker These should be excluded when one is evaluating effectiveness of the waveform analy

Table V Analysis of status of batteries of pace makers removed at first detectable change in waveform study

Finding	*No.*	*Battery status*	
		Failing	*Normal*
I	54	46	8(15%)
IA	5	5	0
ID	1	1	0
IDA	2	2	0
Sensing failure	3	0	3
	65	54	11(17%) (false positive)

I = interval A = amplitude D = impulse duration.

sis technique as illustrated in Table IV It should be noted that defects other than battery exhaus tion may also be detected these include wire fracture high threshold, electrode malposition and miscellaneous other items Table III indi cates the relative frequency of battery exhaus tion over the past four years There has been lit tle change during that time with battery ex haustion accounting for approximately 81 per cent of all replacements

As indicated, the most important parameters for detecting battery exhaustion were impulse in terval amplitude and duration and combina tions of these With some pacemakers failure of sensing was also indicative of battery exhaustion. In an effort to clarify the importance of the various parameters pacemaker battery failure was examined retrospectively with regard to the first abnormal finding detected in the clinic (Ta ble V) If change of rate were selected as the only index of failure eight of 54 pacemakers (15 per cent) would have been removed prematurely On the other hand, when two changes had occurred simultaneously (Table VI) only two of 36 (5 5 per cent) were removed prematurely and none was removed late Based upon analysis of explanta tion life of these units, Fig 4 suggests that it is safe to wait for a second change to occur With one change only the output was usually over 6 volts, or nearly normal. But with two or three changes the output voltage fell to 5 volts or more than one cell failed, in 80 per cent of cases. These

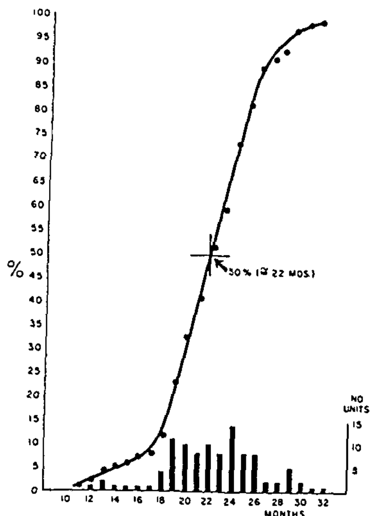


Fig 3 Battery life of Cordis Ectocor 129E including only those units *removed* for battery exhaustion during 1971 72 Routine pulse generator replacement at 18 or 20 months would have meant premature operation in most patients.

and ECG Although this technique has been a more recent development it is less complex than a standard pacemaker clinic and therefore should be discussed first. Phone monitoring is attractive because it permits evaluation of the pacemaker at any time of night and day with little physical inconvenience to patient or technician, but it is limited by the type of information that can be transmitted over the telephone It is relatively simple to transmit the pacemaker rate and even the ECG but not the impulse amplitude or duration In order to transmit the latter the electrical impulse first must be converted to digital information by a phone device in the patient s home Such a service is available commercially (see Appendix A)

Under usual circumstances detecting the pacemaker rate is accomplished with a device that uses ECG type electrodes either held by hand or placed in the axilla Other devices detect the radiofrequency signal produced by the pacemaker Several of these systems are also available

An early objection to transtelephone surveillance was the inability of the observer to determine if the pacemaker impulse was actually pacing the heart. Two methods to correct this difficulty have been developed. One system transmits a peripheral pulse in addition to the signal from the pacemaker This physical pulse is detected by an optical transducer at the finger tip The transducer also doubles as one of the ECG sensing electrodes The other more obvious and perhaps preferable method is to transmit an ECG simultaneously (Appendix A)

When transtelephonic monitoring is performed as the only method of surveillance, it fails to provide some of the desirable attributes of a clinic such as a normal doctor patient relationship, the opportunity to examine the patient, and the ability to study the waveform in depth It does however, permit conversation between a technician or physician and the patient, which is obviously better than no contact whatever It also provides the clear advantages of communication over long distance *if necessary*, opportunity for frequent re examination and less expense [14] The use of a telephone system to *augment* the waveform analysis method combines the attributes of each

Commerical devices. Two companies in the United States will provide telephone monitoring as a service Experience has shown that the quality of the test and personal service have been good [15,16] Its value, in my opinion, is limited by lack of direct contact with the responsible physician and by the implied shift of responsibility to a third party Nevertheless service may be useful in certain clinical and geographic settings

Pacemaker clinics A detailed review of the history and development of pacemaker clinics may be found elsewhere [4,8,10,11] The clinic at the Newark Beth Israel Medical Center is characteristic of most except for the extent of its organization, the integration of eight affiliated centers using a common computer program and the use of a computer itself

In brief, the clinic performs waveform analysis at regular intervals during the life of the pacemaker Toward the end of life where more frequent observation *is required* transtelephone

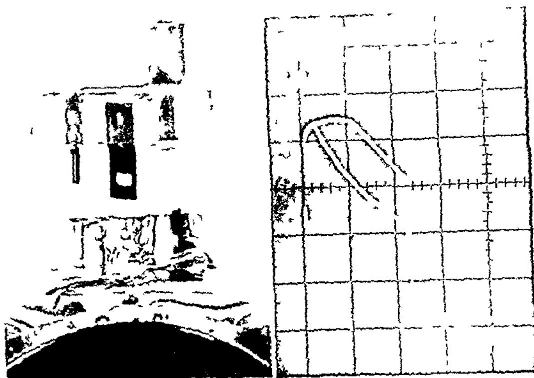


Fig 5 Photograph of connector of Cordis pacemaker with broken connecting pin (left) This was detected by noting a sudden alteration in waveform (right)

unexplained rate change of 40 msec immediately after implantation and a rather steady rate change thereafter not accompanied by a drop in amplitude Telephone monitoring was instituted in addition to periodic regular clinic visits. Not until there was co existent change in the pulse amplitude was this pacemaker replaced. Its useful implantation life was thus extended from a few weeks to almost 21 months

The relative importance of the three parameters—interval, duration and amplitude—is shown is Table X. Retrospective analysis of pacemakers removed for verified battery exhaustion over three years indicates that change in pulse interval occurs in almost 100 per cent of cases and amplitude in 80 to 85 per cent.

The importance of impulse duration is not clear because the design of pacemakers seems to change from year to year also until now the impulse duration has in most cases been designed to be quite stable *

* Recently several new pacemakers have been designed that increase the pulse duration as the batteries become exhausted near the end of life. Thus measurement of the pulse duration may assume greater importance in the future.

Table IX False negative errors in diagnosis of impending pulse generator failure during past four years

	1969	1970	1971	1972
No of cases	74	82	70	85
Errors	7	5	1	3
Per cent correct	91	94	99	96 5

Impulse amplitude should directly reflect the battery voltage This measurement has been hard to evaluate because of the wide range of values noted from month to month As the pacemaker pocket matures the pacemaker will migrate somewhat this will change the apparent amplitude of the pacemaker impulse because it is a vector force In the last two years we have begun to wrap all pacemakers in a cloth pouch which maintains the position of the pacemaker against the pectoral fascia [17] Fig 7 indicates the relative stability of the amplitude value in two groups of patients examined prospectively over

Table VI Battery voltage according to clear clinic findings

Finding	No	Battery status	
		Failing	Normal
IA*	15	14	1
ID	1	1	0
IDA	19	19	0
IDAS	1	0	1
Total	36	34	2(5 5%) (false positive)

I = interval A = amplitude D = impulse duration S = sensing circuit.

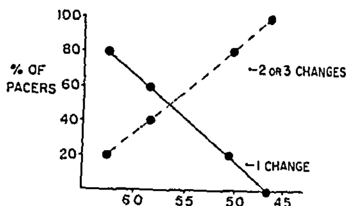


Fig 4. Relationship of the number of findings (change in im pulse amplitude duration and interval) to battery voltage Note that with a drop in one cell (about 5 volts) two or three changes are usually seen and that this occurs only rarely when battery voltage is greater than 6 0

Table VII Life cycle longevity of explanted pulse generators

Output voltage at start of test (1 000 ohms)	No of units	Longevity	
		Average	Range
5 0 5 9	22	5 3	2 5 10
3 5 4 9	6	3 9	1 10

Table VIII Present criteria for pulse generator replacement for battery exhaustion*

Findings	Recommended action	
	Pacemaker dependent	Not pacemaker dependent
Change in interval only	Replace within 4 to 6 wk.	Wait for second finding
Change in interval and duration or amplitude	Replace im mediately	Replace within 2 to 4 wk.
Sudden failure of sensing circuit	Probably will not be detected	Replace at leisure if isolated finding replace soon if associated with interval or ampli tude change
Loss of capture	Replace im mediately	Replace im mediately

Interval clear change in rate of change duration ± 0 2 msec amplitude drop of 15 per cent below lowest previous reading

pacemakers also continued to function for 2½ to 10 months in a body temperature saline bath, even though the battery voltage had dropped to 3 5 or 4 9 volts before the start of the test (Table VII) The first total failure of a pacemaker was one month later in the saline bath [3*] On the ba sis of tests of this kind, criteria for pacemaker replacement have been revised (Table VIII) The criteria depend partly on whether or not the pa tient is pacemaker dependent. Obviously, if the patient can be expected to have cardiac arrest if the pacemaker fails, the criteria for removal must be strict.

False negative tests are now uncommon In 1972 96 5 per cent of battery exhaustion cases were accurately predicted Before then most er rors occurred before the detailed week by week telephone surveillance was instituted, the addi tion of telephone surveillance has almost elimi nated these errors (Table IX)

Examples of the advantages of a complete clinic analysis may be seen in Table IV, where other forms of pacemaker systems failure are also listed Fig 5 illustrates a broken pin in a Cor dis pacemaker that was detected by a beat to beat change in a waveform

Another type of benefit that the waveform clinic method allows is illustrated in Fig 6 Here it was possible to keep a pacemaker implanted despite early and striking changes in impulse in terval One can see that there was a sudden

These data are important only for the specific pulse generator under study For example although the same criteria for replacement were used with the Medtronic 5841 the first failure occurred 15 days after removal

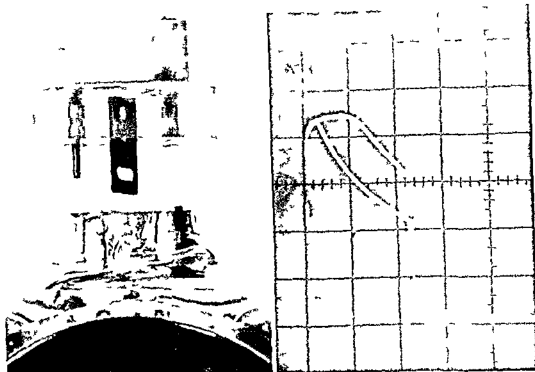


Fig 5 Photograph of connector of Cordis pacemaker with broken connecting pin (left) This was detected by noting a sudden alteration in waveform (right)

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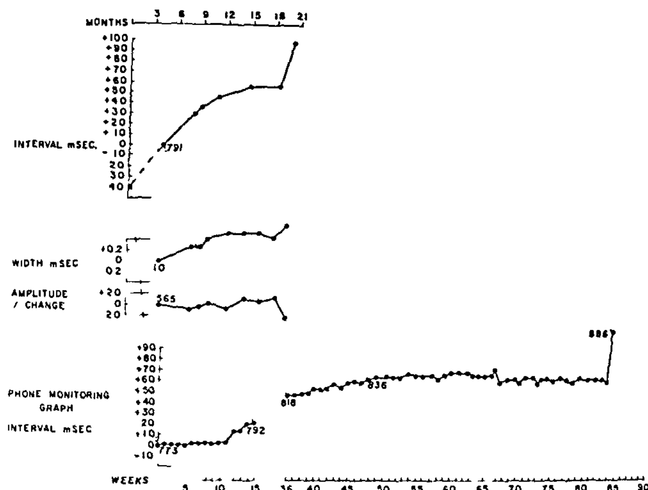


Fig 6 Illustration of how the judicious use of telephone monitoring of interval as well as waveform analysis extends pacemaker life. The pulse generator implanted at a rate of 72 beats per minute jumped to a rate of 80 within a few days Thereafter progressive rate changes were noted and followed for two separate periods by phone and clinic evaluation On the basis of the stable amplitude level the pulse generator was left in place for 21 months Use of the phone system alone would have dictated replacement of the pulse generator immediately

Table X Relative frequency of changes in impulse interval, duration, and amplitude seen during the past three years

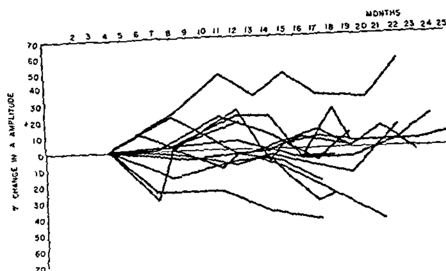
	1970 *80 cases*	*1971* *69 cases*	*1972* *85 cases*
Interval	67(84%)	69(100%)	85(100%)
Duration	58(73%)	16(23%)	31(36%)
Amplitude	57(71%)	59(86%)	68(80%)

the past 24 months The amplitude measurements of the pacemakers wrapped in cloth were more stable Therefore one can rely more heavily on a drop in amplitude as an index of drop in battery voltage

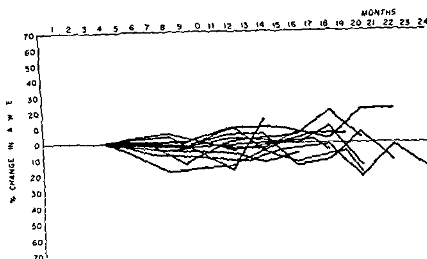
In actual clinic operation, especially in a clinic where a great many different model pacemakers are used, it is difficult to remember the failure modes of all pacemakers To assist us in this problem we have made diagrams that can be kept up to date as new information is acquired. An example of this is illustrated in Fig 8 Once sufficient data of this type have been secured, the computer will be programmed to indicate a change in pacemaker function

Although the advantages of a waveform clinic have been stressed, disadvantages do exist. The method is somewhat more expensive than other systems, although it is still well within an acceptable range Analysis of pacemakers with bipolar electrodes is somewhat more difficult, particularly with respect to amplitude of the impulse However, there is no satisfactory substitute when bipolar electrodes are used because transmission over the telephone is also difficult Utilization of the radiofrequency emission may be helpful in cases of this sort unless the pulse generator has been shielded by an all metal case

In handling large groups of patients the clinic



NO POUCH
(13 PTS)



POUCH
(12 PTS)

Fig 7 Wrapping a unipolar pulse generator in a cloth pouch prevents migration and increases the value of unipolar amplitude readings as an index of battery voltage

method provides great efficiency in patient care For example, at the Newark Beth Israel Medical Center 30 to 40 patients are seen in a two hour clinic each week The computer now maintains records produces a report indicating waveform changes and trends, and generates a letter to the referring physician indicating the status of the pacemaker and explaining the findings on the report form Further refinement in computer programming may eventually allow direct analog to digital conversion of the measurements from the testing equipment and further simplify the clinic operation.

An unexpected but pleasant spin off of the clinic has been the development by the patients of a Pacemaker Foundation This group has organized to help its members learn to cope with implanted pacemakers to support each other in efforts to lead useful and productive lives and to help new pacemaker patients over the initial psychologic and physical burdens that confront them

Within the past year the Pacemaker Foundation has developed associated foundations throughout the United States and Canada and has begun to raise funds for pacemaker research

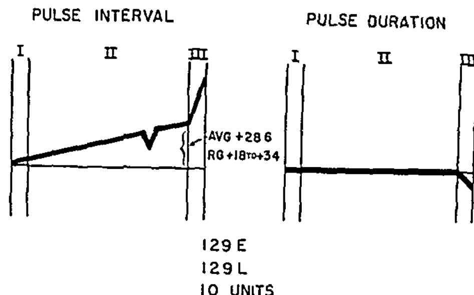


Fig 8. Diagram used to assist in making judgments in the clinic This diagram can be up-dated as new information is acquired. On the left is shown the rate of change of the pulse interval over the pacemaker life. The dotted line indicates the range and area III indicates the typical failure mode Pulse duration change is also indicated at the right in this case the typical change that can be expected is seen in the heavy line and the variations in the light line Amplitude changes are not indicated because amplitude always decreases at end of life Once sufficient data of this type have been secured, the computer will be programmed to indicate the significant changes in pacemaker function

Summary

A waveform analysis clinic augmented by telephone transmission of pacemaker interval in the late stages of pacemaker life will yield a considerable amount of information and will permit elective replacement of pacemakers in about 90 per cent of cases The clinic has an advantage over other surveillance systems in the accuracy of the diagnosis the identification of abnormalities that do not require pacemaker replacement, and the multiple benefits of a direct doctor patient relationship

No system of surveillance can be recommended over all others in all circumstances. It is sufficient here to indicate the merits of each system and to allow the various centers to develop according to their particular needs and desires There is no objection to telephone monitoring alone as long as one realizes that only about 80 per cent of the problems will be detected and that there will be an irreducible percentage of false negative and false positive diagnoses The danger of errors of this type is not great but it does exist and should be avoided if possible Other methods of pacemaker follow up such as simple examination and an ECG in a doctor's office, or changing the pacemaker on the basis of the manufacturer's prediction, are relatively unsatisfactory

It should be stressed that pacemaker surveillance of some type is essential to satisfactory patient care because it provides for maximum utilization of the pacemaker, for replacement only if and when necessary, for detection of 90 per cent of pacemaker problems, and for protection of the patient against unexpected pacemaker failure

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Appendix A

Available equipment	*Function of equipment*
I Phone devices	
ESB Inc 19 West College Ave Yardley Pa.	Interval only Interval and ECG
Paramedic Instrumentation, Ltd. 2184 W Broadway Vancouver 9 B C Canada	Interval only Interval and ECG
Monsanto Electronics Instruments 620 Passaic Ave West Caldwell, N J	Interval only
Computer Instruments Corporation 92 Madison Ave Hempstead L. I N Y	Interval and ECG
II Proprietary phone services	
Cardiac Datacorp Inc 1705 Walnut St. Philadelphia Pa.	Interval plus peripheral pulse
Pacemaker Diagnostic Clinic of America 4020 W Newberry Blvd. Gainesville Fla.	Interval, amplitude impulse area, and ECG
III Phone devices supplied by manufacturers	
Edwards Laboratories 17221 Red Hill Ave Santa Ana Calif	Interval only
General Electric Company 4855 Electric Ave Milwaukee Wis.	Interval only
IV Waveform analysis	
Hewlett Packard West 120th Century Rd. Paramus, N J	Interval, amplitude pulse duration, contour photo ECG
Gutman, LPM 8191 Eurasburg (Obb.) Germany	Interval pulse duration, automated card punch. Phone system also available
Ryden device	

*The reader is ref rred to the original article.10 This device may not be ava lable in the Un ted States.

Contralateral effects of cardiac disease affecting primarily either the left or right chambers of the heart

Allen B Weisse, M D
Newark N J

Physicians have long been intrigued by the possible effects that disease on one side of the heart might induce on the other A number of cardiac diseases have involved this question and, therefore, form a group of conditions within a common frame of reference which to our knowledge have not been so treated in previously published reviews or discussions

Basic considerations

Whether one subscribes to the concept that the ventricular musculature is arranged into four bands[1] two functional bundles[2] or no discrete groups of muscle at all,[3] it is generally agreed that the myocardium constituting the ventricles forms an anatomical continuum around these chambers both in man and in his experimental mammalian surrogates, the dog cat, etc[3] This anatomical arrangement has suggested a functional relationship which has been demonstrated in experiments such as those in which over 75 per cent of the canine right ventricle has been cauterized with no significant change in central venous or systemic pressures[4,5] those involving experimental right heart overload or failure in which left heart sarcomere lengths were increased[6] left ventricular contractility was adversely affected,[7] LV collagen was increased,[8] and various other LV biochemical abnormalities resulted[9,10], those in which aortic constriction resulted in depletion of right ventricular, as well as left ventricular, norepinephrine stores[11] and those in which the distensibility of one ventricle was shown to be dependent upon the filling of the other[12]

The degree to which the hypotheses of such experimental studies have been substantiated in human cardiac disease and the mechanisms involved form the basis of the subsequent discussion

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Right heart effects of left heart disease

Right heart failure in ischemic hypertensive and rheumatic heart disease Before human intracardiac pressure measurements were available Harrison, in his monograph on heart failure, postulated that in the majority of instances failure of the right ventricle is brought about by the increase in the pulmonary vascular pressure consequent to failure of the left side of the heart[13] A few years later in 1946, the New York University Columbia Bellevue group published right heart studies in 70 patients, the majority of whom had chronic pulmonary disease[14] Only one case of arteriosclerotic and five cases of hypertensive cardiovascular disease were included, in only one of which were right heart pressures elevated There were, however, eight cases of rheumatic heart disease with obviously high right ventricular systolic pressures in five which led them to conclude that right ventricular systolic and pulse pressures are '*markedly elevated* in *all* cases of primary left heart failure *regardless of etiology*'[14] (my italics)

This concept does not seem to be borne out by the facts Let us consider ischemic heart disease (IHD), hypertensive cardiovascular disease and rheumatic heart disease separately

When florid right heart failure complicates

Table I Pathologic studies in ischemic heart disease

Authors	*No of infarcts*	*% infarcts involving*		*Other cardiac diseases*			*RV histology*
		RV only	*LV & RV*	*Septum*	*Noted*	*Analyzed separately*	
Appelbaum & Nicolson, 1935[25]	117	6	6	16	—	—	—
Wartman & Hellerstein, 1948[6]	235	14	—	38	+	—	—
Wang et al 1948[27]	556	2	—	53	—	—	—
Yater et al., 1948[28]	153	5	—	26	+	—	—
Miller et al. 1951[29]	*143†*	—	—	—	+	—	+
Snow et al 1955[30] 1956[31]	59	3	—	—	—	—	+
Laurie & Woods 1963[32]	90†	4‡	—	—	—	—	+
Ehrlich & Shinohara, 1964[33]	38†	0	50	—	—	—	—
Fulton, 1965[34]	25†	0	64	68	+	+	—

Abbreviations. RV = right ventricle LV = left ventricle + = yes, — = no or information not provided.
Includes those with free RV plus septal involvement.
†Hearts.
‡*Gross infarcts 37 per cent using microscopy*

IHD right heart pressures are usually only moderately elevated and rarely at or near systemic levels In 33 such patients studied acutely collected from our own files and the literature[15-19] the average systolic pressure *in the* right ventricle or pulmonary artery was 46 ± SEM 2 mm. Hg *with none above 80 mm Hg*

In contrast it should be noted that in a long *term study of a large number of cases of isolated* pulmonic stenosis with pure right ventricular pressure loading no patients with RV systolic pressures below 80 mm. Hg and only five per cent in the range of 80 to 119 mm Hg developed heart failure[20] The same applies to patients with idiopathic or thromboembolic pulmonary hypertension[21]

It might be reasoned that in IHD with heart failure the decrease in cardiac output might result in a lowering of RV systolic and pulmonary artery pressure so as to make the degree of pulmonary hypertension less apparent. However when such patients are studied following clinical compensation these pressures with few *exceptions are still only moderately elevated.*[15,22]

In view of the above findings one is drawn to a *consideration* of the extent of direct right ventricular involvement in IHD The consensus *of opinion* in the past has been that this is rare with isolated RV infarcts constituting less than two per cent.[23,24]

In frequently cited pathological studies of IHD reviewed[-5,34] (Table I) RV weight was measured in only one[6] and *consideration of heart failure* was omitted in all. However the data suggest *that routine RV histological* examination might uncover involvement not apparent on gross examination[32,33] and to a much greater extent than had been previously thought to exist[35,36] From Table I it should also be noted that if the septum is considered part of the RV wall the percentage of right heart involvement in myocardial infarction may range as high as *50 to 60* per cent.

In IHD it thus appears right heart failure might be due to a greater degree of RV involvement than has previously been recognized. *Another possibility* since a severely cauterized right ventricle does not result in appreciable venous congestion in the presence of a normal left ventricle[4,5] is that right heart failure in IHD may be precipitated by failure of the contiguously diseased left ventricle *Alternatively* experimental partial occlusion of the coronary arterial *supply to the right ventricle results in no* dysfunction until the addition of a pressure load.[37] In human *coronary* artery disease the modest pressure load reflected from the left side of the heart combined with a compromised blood flow to the right ventricle may cause its decompensation. Finally metabolic and biochemical abnormalities such as norepinephrine depletion

in the right heart consequent to left ventricular failure[38] may help precipitate RV failure

In hypertensive cardiovascular disease (HCVD) with right heart failure the case for the back pressure theory is also weak Although RV weight is somewhat increased following congestive heart failure,[35 39 40] right heart pressures in decompensated HCVD are not significantly different from those in IHD [16 41 43] Furthermore, when congestive heart failure supervenes, the situation is complicated by the high incidence of other forms of heart disease co existing Between 50 and 60 per cent of patients with HCVD and heart failure may also have IHD with only three per cent of such patients without other precipitating causes [44]

In rheumatic heart disease alone, where mitral valve involvement gives rise to severe pulmonary hypertension even in the presence of low flow rates can one support the view of a direct relationship between this and right heart failure

Right heart reflections of left heart pressures in acute myocardial infarction In acute myocardial infarction the main hemodynamic abnormalities involve the left heart with predominant right heart derangements rare and only recently documented [45] During the past few years many reports have appeared concerning the validity of right heart pressure measurements as reflections of left heart pressures in acute myocardial infarction Their results summarized recently [46] appear to indicate that both in man and the dog in acute infarction of a previously normal left ventricle the normal equivalence of the pulmonary artery end diastolic pulmonary capillary wedge left atrial and left ventricular end diastolic pressures is maintained However a left ventricle with a previous scar or other abnormality may develop end diastolic pressures much higher than the other pressures following acute myocardial infarction Furthermore pulmonary vascular obstruction from any cause and severe tachycardia may result in pulmonary artery end diastolic pressures higher than those recorded in the wedge position or left atrium

The Bernheim syndrome Perhaps the earliest report of one ventricle interfering with contralateral function was Bernheim s description of a group of cases characterized by left ventricular hypertrophy with bulging of the septum into the right ventricle, interfering with its filling and resulting in systemic venous congestion [47 48] A number of clinical reports of this syndrome have appeared,[49,50] but only one hemodynamic study prior to death by Selzer and associates,[51] who were unconvinced of the validity of this entity as were Evans and White[52] some years earlier Recent fuel to the controversy has been added by the report of Epstein and colleagues[53] of the great frequency of gradients between the apex and the body of the right ventricle in aortic valvular disease Right ventricular gradients may also occur in cardiomyopathies, possibly by the hypertrophic process involving the right ventricle itself,[54,55] or possibly related to LV septal encroachment.[56 57] Although Bernheim used the term stenosis interference to filling in the lower portion of the right ventricle was the mechanism of dysfunction inferred and not obstruction to emptying, as described in these recent studies. A review of Bernheim s case summaries raises serious doubts that any fall into either category, and description of the syndrome as such should probably be discarded.

Left heart effects of right heart disease

Chronic cor pulmonale Evidence of left ventricular involvement in chronic cor pulmonale (CCP) originally derived from pathologic reports of left ventricular hypertrophy in such patients Interest was further stimulated by the finding of apparent LV dysfunction in the high altitude pulmonary hypertensive heart disease of cattle ('Brisket Disease") formerly thought of as a naturally occurring form of pure right heart disease [58] On the heels of this work several human physiologic studies of the left ventricle in CCP patients have appeared The following questions will be considered (1) Does left ventricular hypertrophy (LVH) result from chronic cor pulmonale? (2) What possible mechanisms might lead to LV hypertrophy and/or dysfunction in CCP? (3) What physiologic evidence is there for LV dysfunction in CCP?

Pathologic data in the studies repeatedly cited in the literature regarding the question of LVH in CCP are summarized in Table II [59-67] Opinions vary and the criteria used by different authors are often non objective or subject to a great deal of measurement error (e g , the criterion of what represents a thickened left ventricle varies no definite uniformity of site of measurement in the

Table II Pathologic evidence for left ventricular hypertrophy (LVH) in cor pulmonale

Authors	No of patients	Heart failure indicated	Incidence LVH (%)	Criteria for LVH
Kountz et al. 1936[59]	17	No	60	Increase LV weight vs. normals
Parker 1941[60]	32	No	34	Visual impression, scale 0 to 4
Scott and Garvin 1941[61]	50	Yes	90	LV thickness ≧ 12 mm
Spain and Handler 1946[62]	60	No	?	Statement that LV was hypertrophied no measurements
			0	Statement no LVH on autopsy
			93	LV thickness ≧ 12 mm
			78	LV thickness ≧ 15 mm
			94	LV thickness 10 to 20 mm
			0	Statement LV free wall comparable to normals
			25	LV thickness ≧ 17 mm

shown to affect LV function adversely [72] Although red cell volume is increased in hypoxia secondary to chronic obstructive airway disease marked elevations in hematocrit which might lead to increased viscosity interfering with blood flow are rare due to plasma volume increases, [3] and even when present may in part at least be offset by the effects of hypervolemia as seen in polycythemia vera [4]

In hemodynamic studies performed in CCP patients both elevation of resting LVEDP [5] and its absence[16] have been reported, but the use of this alone as an indication of LV function is now well recognized to be inadequate Evaluating LV function by increasing afterload, Williams and associates [77] using methoxamine did not find evidence of LV dysfunction in CCP while Baum and co workers [78] using angiotensin showed a decrease in LV performance in their CCP patients Apparently the group studied by Baum and co workers[78] were more disabled (more abnormal blood gas values and initially elevated LV end diastolic pressures) The use of angiotensin which may affect contractility adversely [79] may also have influenced the results of Baum and co workers

Our own approach involved resting and exercise studies in CCP patients[80] in whom LV contractile state was found to be normal, although cardiac index stroke work and ejection fractions were subnormal. We attributed the latter findings more likely due to age difference between patients and controls not necessarily indicative of LV dysfunction An alternative explanation could be that LV stroke work *etc* was limited by the diminished function of the right ventricle [81]

The possibility of associated left ventricular disease will continue to challenge the clinician

Whether hypertrophy alone leads to ventricular dysfunction is, of itself, a matter of some controversy and beyond the scope of the present discussion.

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In rheumatic heart disease alone, where mitral valve involvement gives rise to severe pulmonary hypertension even in the presence of low flow rates can one support the view of a direct relationship between this and right heart failure

Right heart reflections of left heart pressures in acute myocardial infarction In acute myocardial infarction the main hemodynamic abnormalities involve the left heart with predominant right heart derangements rare and only recently documented[45] During the past few years many reports have appeared concerning the validity of right heart pressure measurements as reflections of left heart pressures in acute myocardial infarction Their results summarized recently,[46] appear to indicate that both in man and the dog in acute infarction of a previously normal left ventricle the normal equivalence of the pulmonary artery end diastolic pulmonary capillary wedge, left atrial and left ventricular end diastolic pressures is maintained However, a left ventricle with a previous scar or other abnormality may develop end diastolic pressures much higher than the other pressures following acute myocardial infarction Furthermore pulmonary vascular obstruction from any cause and severe tachycardia may result in pulmonary artery end diastolic pressures higher than those recorded in the wedge position or left atrium

The Bernheim syndrome Perhaps the earliest report of one ventricle interfering with contralateral function was Bernheim's description of a group of cases characterized by left ventricular hypertrophy with bulging of the septum into the right ventricle, *interfering with its* filling and resulting in systemic venous congestion[47,48] A number of clinical reports of this syndrome have appeared,[49,50] but only one hemodynamic study prior to death by Selzer and associates[51] who were unconvinced of the validity of this entity, as were Evans and White[52] some years earlier Recent fuel to the controversy has been added by the report of Epstein and colleagues[53] of the great frequency of gradients between the apex and the body of the right ventricle in aortic valvular disease Right ventricular gradients may also occur in cardiomyopathies, possibly by the hypertrophic process involving the right ventricle itself,[54,55] or possibly related to LV septal encroachment.[56,57] Although Bernheim used the term stenosis, interference to filling in the lower portion of the right ventricle was the mechanism of dysfunction inferred and not obstruction to emptying, as described in these recent studies. A review of Bernheim's case summaries raises serious doubts that any fall into either category, and description of the syndrome as such should probably be discarded.

Left heart effects of right heart disease

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Table II Pathologic evidence for left ventricular hypertrophy (LVH) in cor pulmonale

Authors	*No of patients*	*Heart failure indicated*	*Incidence LVH (%)*	*Criteria for LVH*
Kountz et al 1936[59]	17	No	60	Increase LV weight vs. normals
Parker 1941[60]	32	No	34	Visual impression scale 0 to 4
Scott and Garvin 1941[61]	50	Yes	90	LV thickness ≧ 12 mm
Spain and Handler 1946[62]	60	No	?	Statement that LV was hypertrophied, no measurements
Harvey et al 1951[63]	8	No	0	Statement no LVH on autopsy
Zimmerman & Ryan, 1951[64]	52	No	93	LV thickness ≧ 12 mm.
			78	LV thickness ≧ 15 mm
Michelson 1960[65]	32	No	94	LV thickness 10 to 20 mm
Bove and Scott, 1966[66]	*	No	0	Statement LV free wall comparable to normals
Flu k et al 1966[67]	84	No	25	LV thickness ≧ 17 mm

*Not analyzed separately

left ventricle is employed, and in only one study was there a concurrent group of control hearts[67]) Furthermore clinical information is ordinarily absent or extremely limited.

It appears however that in some patients with CCP some degree of LVH probably exists but the true incidence of and reasons for this are poorly defined.*

Some believe that hypertrophy of the right ventricle ultimately leads to a similar process in the left because of their anatomical continuity[63] Because bronchopulmonary anastomoses have been demonstrated at autopsy in patients with chronic obstructive pulmonary disease[68] it was once thought that these left to right shunts might produce a volume overload for the left ventricle and thus lead to its hypertrophy However a large series reviewed and added to by Wade and Bishop[69] refuted this More recently attention has focused on metabolic factors (hypercapnia acidosis hypoxia) and polycythemia. Experimentally hypoxia and acidemia especially when acting in concert, have been shown to affect LV function adversely [0 72] Although red cell volume is increased in hypoxia secondary to chronic obstructive airway disease marked elevations in hematocrit which might lead to increased viscosity interfering with blood flow are rare due to plasma volume increases[73] and even when present may in part at least be offset by the effects of hypervolemia as seen in polycythemia vera[74]

In hemodynamic studies performed in CCP patients both elevation of resting LVEDP[75] and its absence[76] have been reported, but the use of this alone as an indication of LV function is now well recognized to be inadequate Evaluating LV function by increasing afterload, Williams and associates[77] using methoxamine did not find evidence of LV dysfunction in CCP while Baum and co workers[78] using angiotensin, showed a decrease in LV performance in their CCP patients Apparently the group studied by Baum and co workers[78] were more disabled (more abnormal blood gas values and initially elevated LV end diastolic pressures) The use of angiotensin which may affect contractility adversely[79] may also have influenced the results of Baum and co workers

Our own approach involved resting and exercise studies in CCP patients[80] in whom LV contractile state was found to be normal, although cardiac index stroke work and ejection fractions were subnormal. We attributed the latter findings more likely due to age difference between patients and controls not necessarily indicative of LV dysfunction An alternative explanation could be that LV stroke work etc was limited by the diminished function of the right ventricle[81]

The possibility of associated left ventricular disease will continue to challenge the clinician

*Whether hypertrophy alone leads to ventricular dysfunction is, of itself a matter of some controversy and beyond the scope of the present discussion.

faced with the decompensated CCP patient presenting with many findings suggestive of LV failure When true LV dysfunction is present in CCP, we believe the greatest likelihood to be that intrinsic disease of the LV coexists. Particularly suspect because of the advanced age of many of these patients would be ischemic heart disease, but although coronary atherosclerosis is common in such patients, the incidence of myocardial infarction is substantially less than that of the general population[82] and probably related to increased coronary collaterals after long standing hypoxia [83] Furthermore, several studies[60 84 85] have shown LV blood flow and oxygen consumption within normal limits in CCP A more likely coexistent left ventricular disease may be cardiomyopathy due to alcohol because of the frequent association noted between alcoholism and lung disease [86]

Conclusions

Despite a quarter century of right heart catheterization in man and over a decade since the introduction of left heart techniques, the pathophysiology of left right heart interrelationships in many common disease states remains to be clearly defined The current status of knowledge in several of these conditions has been reviewed

In recent years better methods have been developed to measure contractile state of the heart, ventricular volumes and performance both by invasive and non invasive means These techniques, combined with coronary arteriography, flow and metabolic measurements, and supplemented by refined histological (electron microscopy) and biochemical examinations of tissue should enable further clarification of these issues, both in the laboratory and at the bedside in future investigations

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Thrombosis, atherosclerosis, and endothelium

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Over the years many investigators have related the pathogenesis of atherosclerosis to thrombosis[1-3] atherosclerotic lesions are well known as sites of predilection for thrombus formation [4] Recently there has been increasing recognition that the state of the endothelium bears a pivotal relationship to both of these pathological processes Thus any condition leading to loss of endothelial cover in a susceptible vessel may be followed by a thrombotic deposit at that site which can attain sufficient growth to compromise blood flow If the vascular lesion is not followed by occlusive thrombus formation, the intimal healing process may be so exuberant that an arteriosclerotic plaque an atherosclerotic precursor may be produced. The following discussion will expand these considerations as applied to arterial disease and hopefully will suggest prophylactic or therapeutic possibilities At this point, the authors wish to offer the following caveat. The present essay is not intended as a comprehensive review of thrombosis and atherosclerosis. Rather it emphasizes a particular point of view some of which is supported only by reasonable hypothesis Many of the data cited herein represent results of animal experiments and their application to human disease remains to be established. Finally it will be evident that no discussion of the role of lipid metabolism has been included, because we feel that this subject has been abundantly covered in a myriad of publications elsewhere

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Factors rendering an artery thrombogenic

As defined in this essay thrombogenic is taken to mean the ability to accumulate hemostatic deposit from flowing blood. This deposit consists mainly of platelets and fibrin erythrocytes are presumably passive and present by virtue of trapping leukocytes are thought by some workers to contribute clot promoting activity [5,6] A surface which is non reactive to blood hemostatic elements is non thrombogenic

The normal blood vessel is completely covered with a carpet of endothelial cells and these present a non thrombogenic surface It would appear that even injured endothelial cells are non thrombogenic and that this state persists until cells come off and underlying connective tissue is exposed. Nevertheless endothelial cells possess a thrombogenic potential the significance of which is not clear at present. Tissue factor (thromboplastin) has been identified immunologically on the plasma membranes of endothelial cells [7,8] and although it appears to be unavailable in the normal state damaged cells may have potent procoagulant activity

The connective tissue underlying the endothelial cells, called the subendothelium is a complex and thrombogenic material containing a diversity of connective tissue species In major rabbit arteries several components have been recognized by electron microscopy there are occasional *collagen fibrils* with their characteristic 680 A periodicity *microfibrils* which represent a connective tissue component described relatively recently and which differ from collagen both morphologically and chemically [9] and are imbedded in the internal elastic lamina *vascular basement membrane*, a felt like network of very fine

syndrome with additional evidence of ventricular septal hypertrophy *in* Wolstenhome G E W and O Connor M editors Cardiomyopathies Ciba Foundation Symposium London 1964 J & A. Churchill Ltd. pp 49 69

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In summary then, the factors that should favor thrombus growth to yield obstruction include extensive loss of endothelial cell cover to give a large base of exposed connective tissue components which produce both platelet adhesion and agregation as well as thrombin and fibrin formation and conditions of flow which favor deposition of platelets retention of activated clotting factors and failure to shear off growing thrombotic deposits

The arterial healing response and its relationship to atherogenesis

Often the combination of conditions is such that arterial intimal injury occurs without consequent occlusive thrombus formation Following such an event there is healing and re establishment of the endothelial cover The injury healing response has been studied in several species[16-19] and the findings in all are generally similar Our own experience has been greatest with the rabbit aorta subjected to balloon injury[19] In these experiments balloon catheters were passed into the aortas via the femoral arteries were inflated, and were passed up to the level of the diaphragm and down again This procedure effectively stripped the vessel of virtually all endothelial cells without evident damage to deeper structures as judged by electron microscopy The observations to be discussed were made on aortas from animals which were killed at various intervals after injury and in which circulation had been promptly re established.

Immediately following injury platelets were seen adhering to the exposed subendothelium. By ten minutes there was almost complete coverage, and the platelets were spread out on the underlying connective tissue At this time some areas showed small thrombi but by an hour these had virtually disappeared, leaving a platelet monolayer Evidently there was abortive partial thrombosis followed by shearing off of the protruding platelet masses, and finally what appeared to be either stabilization of the platelet layer or an equilibrium reaction in which only a single thickness platelet layer was permitted to persist. By three hours scattered neutrophils were seen to be accompanying the platelets, and over the next two days these were gradually replaced by mononuclear cells. Of particular interest was the observation that in the large number of rabbits subjected to this aortic balloon injury there was never thrombotic deposition of sufficient magnitude to produce compromised circulation despite the extensive area of vessel which had been denuded of endothelium.

The onset of vascular healing became evident on the third day following injury and this appeared to have been initiated by scattered migration from the media, of smooth muscle cells, through lacunae in the internal elastic lamina so that these cells came to assume a position on the luminal surface In the ensuing days this neointima was enriched by additional smooth muscle cell migration and also by mitotic proliferation of these cells A relatively minor contribution to coverage was made by direct proliferation of endothelial cells which had escaped injury Such cells were those which were located beyond the reach of the balloon catheter above the diaphragm, and also those at the mouths of arterial branches from the aorta By six to seven days after injury the cellular cover of the subendothelial connective tissue had been restored, this now appeared to consist of transposed and transformed smooth muscle cells and is designated the neointima '

A striking feature of the healing intima was the progressive tendency for its cells to proliferate into layers two to several layers deep Even by day four this tendency was evident in focal areas at the end of a week when a cellular cover had been completed this process was virtually universal. Moreover cellular thickening of the intima was a progressive phenomenon so that by four weeks after injury many areas were as thick or thicker than the media. Fig 3 illustrates the histology of a healing rabbit artery following balloon injury the intimal thickening of which shows its resemblance to the arteriosclerotic plaque in man

Even more advanced lesions have been produced in rabbit arteries by other investigators. Indeed a picture resembling human atherosclerosis in rabbits has followed mechanical as well as immunological trauma Moore[20] inserted permanent plastic catheters into aortas and noted that plaques developed at certain sites of catheter vessel contact. Moreover at two months these lesions were lipid laden and this reaction occurred in the absence of special diets or hypercholesterolemia. Minick and co workers[21] administered intravenous doses of horse serum or bovine serum albumin repeatedly and

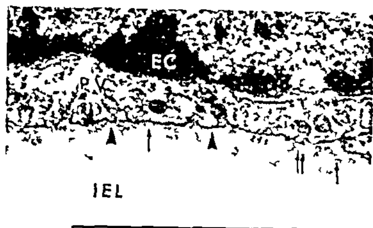


Fig 1 Electron micrograph of rabbit iliac artery in cross section and highly magnified. A portion of an endothelial cell (*EC*) is seen attached to the internal elastic lamina (*IEL*) *The nucleus of the endothelial cell is seen above its* cytoplasm is characterized by numerous rounded pinocytotic vesicles (*PV*) Microfibrils *(dark arrows)* are seen cut in cross section and appear as dense dots Vascular basement membrane *(large arrowheads)* appears to be relatively amorphous in this picture greater resolution being required to demonstrate clearly its filamentous properties (Line denotes 1 micron)



Fig 2 Lines of flow in the presence of a wall abnormality The normal streamlined flow to the left is contrasted to the formation of a trapped vortex after the irregularity is encountered. Blood circulating in the vortex cannot reach the general circulation (From Leonard, E F The role of flow in thrombogenesis, Bull N Y Acad Med. 48 273 1972 Reproduced with permission)

filaments and *elastin*, which is electron lucent. These connective tissues have a reactivity with platelets which appears to be of decreasing intensity corresponding to the order listed.[10] Thus collagen is intensely reactive elastin appears to be virtually inert Fig 1 is an electron micrograph of a rabbit aorta which illustrates these anatomical features It should be noted that the distribution and concentration of the connective tissues varies among the different subendothelia, and is influenced by such factors as species age and endocrine environment For example the prolonged injection of estrogen into rabbits increases the arterial subendothelial content of microfibrils[11] It may be presumed that a vessel with a heavy subendothelial endowment of a more active connective tissue species, such as collagen, will be more thrombogenic when its endothelial cover is lost. These considerations are further complicated by recent observations in our laboratory, which suggest that in normal rabbit vessels, electronlucent connective tissues *(mucopolysaccharides?)* may "insulate' thrombogenic connective tissues, thereby rendering them less active Perhaps these vary under different conditions as well

Of the subendothelial connective tissues collagen and to a lesser degree elastin, have been shown to have procoagulant activity by virtue of their ability to activate Hageman factor (Factor XII)[12] Corresponding data are not available on the other connective tissue components

Another major factor determining thrombogenicity is that which affects flow characteristics The influence of flow can be manifested in several ways. In conditions of extremely slow flow, delivery of hemostatic elements to an injured site may be limiting At the same time such slow flow may permit thrombin and fibrin formation because of sluggish removal of locally formed reactants blood fluidity is favored when activated clotting factors escape into the circulation to be cleared by the liver, reticulo endothelial system, and other organs[13] Thrombin has the dual effect of both clotting fibrinogen and augmenting platelet aggregation Thus in venous disease, thrombi are formed which are rich in fibrin, and which contain trapped whole blood. A second type of flow alteration which may similarly favor blood coagulation is that associated with a sufficient irregularity of the intima such as may be produced by an atheromatous plaque In this case the mechanism is that of a trapped vortex' a condition characterized by local blood recirculation, as illustrated in Fig 2 and fully discussed elsewhere[14] Blood in a trapped vortex is sequestered although it circulates locally, it cannot escape into the general circulation, and it is therefore liable to ultimate clotting Finally, in the presence of extremely rapid flow, hemostatic deposits may form and grow until they are sheared away, leaving a site for repeated small thrombus growth and embolization[15] A damaged blood vessel presenting this type of reaction may not reveal significant thrombus obstruction when examined by angiography or pathologically but it may result in considerable damage downstream in its respective organ

atherosclerosis may be produced by endothelial injury alone hypercholesterolemia appears to be accessory but not essential for significant lipid deposition

The concept of endothelial damage as the initiating event for atherosclerosis is venerable having been introduced by Virchow in 1856[23] He postulated a proliferative reaction as the basis for intimal thickening A greatly modified scheme was developed by Duguid[24] who proposed that intimal thickening resulted from incorporation of mural thrombi and their subsequent invasion by connective tissue In recent years Virchow s original views have received new corroboration as numerous investigators have demonstrated the development of intimal thickening as a response to various types of endothelial insult There is growing evidence that the proliferating intimal cells are smooth muscle cells derived from the media and the suggestion has been made that the basis for migration and proliferation is increased intimal permeability to plasma lipoproteins[25] According to this hypothesis the medial smooth muscle cells respond to the plasma proteins when the latter are presented in concentrations exceeding those normally encountered. If such is the case intimal proliferation would be expected to continue as long as increased permeability persisted. In this connection it is noteworthy that the vessel subjected to a single balloon injury shows marked regression at the end of six months from the maximal degree of thickening seen at one month[16] Perhaps restoration of normal permeability corresponds to the time at which proliferation ceases and regression commences.

Thrombogenic properties of the arteriosclerotic vessel

It is common knowledge that arteriosclerosis and atherosclerosis predispose to thrombosis and that the vascular lesions are sites of thrombogenic predilection Increased thrombogenicity appears to be a property of the arteriosclerotic rabbit vessel as well. When a rabbit aorta is subjected to balloon injury allowed to heal for four weeks, and then ballooned a second time the thrombotic deposit on the areas of fresh injury are significantly increased,[16] as shown in Fig 4 Several features characterize the thrombi in the twice injured vessel as compared to those in the ballooned virgin vessel in the former platelet masses are larger and more persistent there is penetration of the thrombotic deposit into the neointima suggesting that this structure is more spongy and permeable than is the normal intima and there is increased deposition of fibrin particularly in apposition to the vessel wall

The basis for the increased thrombogenicity of the arteriosclerotic vessel is not established but the possibilities may be examined in the light of considerations mentioned earlier (1) No data are available yet concerning the clot promoting activities of either the new connective tissue or the associated neointimal cells but the possibility of enhanced promotion of blood coagulation locally cannot be excluded (2) Electron microscopy of the arteriosclerotic vessel does not reveal increased concentrations of the more thrombogenic connective tissue species and it is not known whether there is a decrease or reduced effectiveness of possible insulating materials. (3) The arteriosclerotic vessel presents configurational changes which must produce deviations from normal streamlined flow If these changes are sufficient the possibility of trapped vortices and consequent failure to clear activated clotting factors locally is likely Moreover the arteriosclerotic vessel is narrowed, a condition producing increased resistance and reduced blood flow thereby favoring the possibility of occlusion It is thus reasonable to conclude that the major impact of arteriosclerosis may well be mediated via those alterations of blood flow which would augment deposition of platelets and evolution of thrombin and fibrin However such flow changes have not been precisely characterized and related to observed events the role of other factors has not been adequately assessed

Therapeutic considerations

The foregoing discussion has indicated considerable interaction between thrombosis arteriosclerosis and atherosclerosis Damage to arterial intima is promptly followed by thrombotic deposition on areas of exposed connective tissue the repair process is associated with long term consequences the most dramatic of which is intimal thickening Additionally thrombotic deposit may further aggravate endothelial damage because of vasotoxic materials released from platelets in the course of adhesion and ag

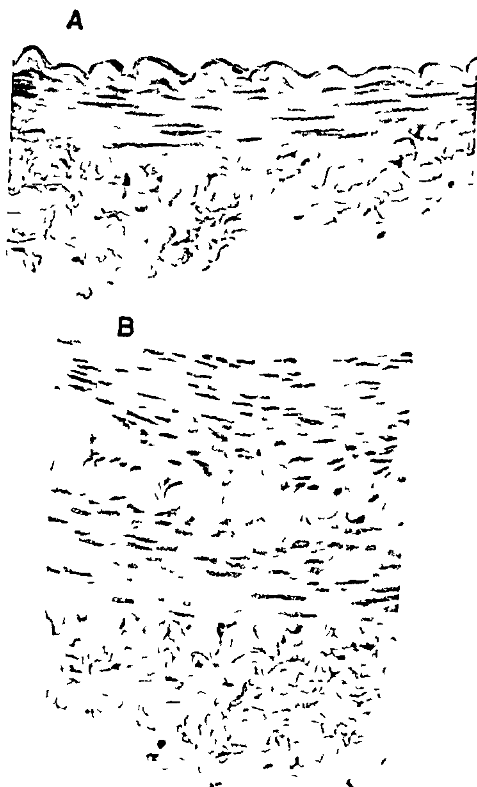


Fig 3 A and B Histological sections of rabbit iliac arteries A *Normal vessel Note the monolayer of endothelial* cells over the internal elastic lamina B One month after healing of balloon injury with intima as thick as media This lesion resembles the human arteriosclerotic plaque (Original magnification × 600)

for many months A few animals subjected to this regimen developed widespread arteriosclerotic plaques In the presence of a normal rabbit diet and without rabbit hypercholesterolemia lipid deposition was encountered in rare lesions mild elevation of plasma cholesterol to usual human levels, by a fat enriched diet, produced lipid laden lesions strikingly similar to those seen in human disease Similar findings were obtained in swine in which endothelial removal produced markedly accelerated development of atherosclerotic plaques in the presence of high cholesterol diets [22] It would appear from these studies that arteriosclerosis and even

munological to toxic Some of these such as hypertension are well recognized others are conjectural or even unsuspected at present Presumably these are almost universal in man if early arteriosclerosis is to be taken as a footprint of previous intimal injury Identification of specific conditions which adversely affect endothelium could lead to appropriate therapeutic responses as illustrated by the early management of hypertension

Control of intimal proliferation Although increased endothelial permeability could be the key to intimal proliferation this phenomenon is by no means well understood at present Delineation of the factors that govern smooth muscle migration and mitotic activity may provide a basis for their control Meanwhile certain data suggest that intimal growth in a damaged vessel may be influenced empirically Wolinsky and colleagues[28] have shown that estrogen reduces aortic hypertrophy in the hypertensive rat. Our own preliminary observations on balloon injured rabbit aortas suggest that estrogen has a significant ability to retard intimal hypertrophy Whether or not these observations lead to therapeutic consequences in human arteriosclerosis they favor the optimistic view that the process of intimal hypertrophy is liable to manipulation and possible control

Antithrombotic therapy It has been mentioned above that platelet thrombi may further damage vessels on which they reside by liberation of vasotoxic materials Similarly emboli from platelet thrombi could produce lesions downstream where they come to lodge [29] These considerations suggest that antithrombotic therapy may lessen the impact and extent of already established vascular damage The newly used agents to inhibit platelet function such as aspirin or sulfinpyrazone may prove to be useful in this respect, although an intensive search for a therapeutically effective platelet inhibitor is in progress

Conclusions

There is growing evidence that a primary vascular lesion is responsible for thrombosis and atherosclerosis. Changes in the state of the blood, such as hypercoagulability or hypercholesterolemia, may influence the degree of the consequences of the vascular lesion and their control may be therapeutically useful However true prophylactic and therapeutic management of arteriosclerosis and atherosclerosis may await better understanding of the primary vascular lesion

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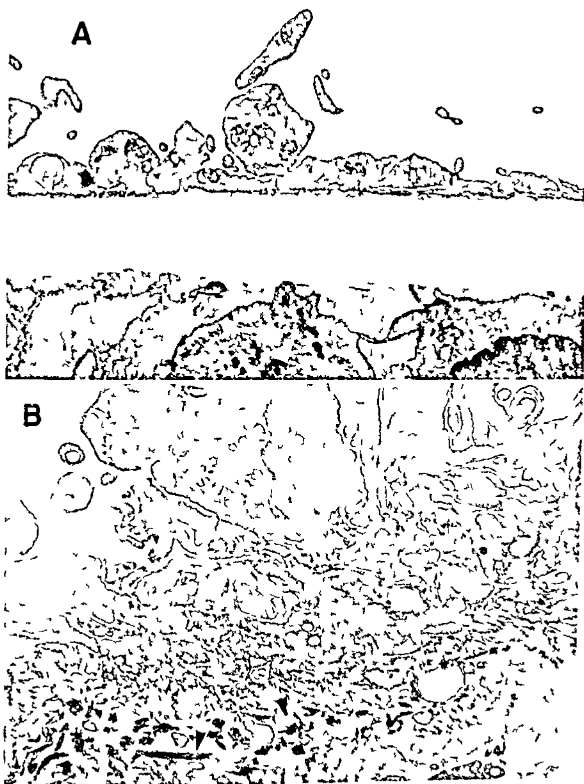


Fig 4 A and B Electron micrographs of balloon injured rabbit aortas processed ten minutes after re establishment of circulation A Vessel subjected to single injury showing essentially a monolayer of platelets coating the subendothelial connective tissue B Vessel subjected to second balloon injury following four weeks of healing after the first. A mass of degranulated platelets is attached to the vessel wall forming a well defined thrombus Note penetration into the underlying connective tissue of platelet cytoplasm and also the appearance of fibrin strands (*arrowheads*) (Original magnification × 32 000)

gregation [26,27] Finally, the vessel which is in the process of healing, or one which is already arteriosclerotic, may be more liable to further intimal injury thereby providing easily produced thrombogenic foci If this picture is relatively accurate, new therapeutic avenues may become available for the prevention of atherosclerosis

Prevention of vascular lesions The blood vessel is potentially susceptible to numerous sources of insult, varying from mechanical to im

Annotations

The management of patients with strokes

Physicians at present too frequently consider the management of strokes to be limited almost entirely to surgery of the large cervical arteries or intracranial aneurysms or to the use of anticoagulants. Little attention is directed to the *prevention of* strokes by use of vasodilators, *maintenance of normal blood pressure,* rest, and other well established principles of preventive therapy. Most strokes are due to cerebral arteriosclerosis and associated arterial hypertension, sustained or paroxysmal.

The Pal's crises (angiospastic crises) seem to be little known and inadequately appreciated. These episodes of relatively minor disturbances in cerebral function of variable extent lasting only a few seconds *to a few minutes are comparable* to the episodes of angina pectoris in ischemic heart disease. These short temporary cerebral ischemic crises are claimed by some to be due to small platelet emboli or emboli originating from arteriosclerotic plaques in proximally located arteries supplying the brain. Pal's crises seem to me to be most often the result of cerebral angiospasm.[1,2] The obstruction to small cerebral arteries is brief and without residual effect. Just as angina pectoris often forewarns of impending myocardial infarction, these attacks of "cerebral angina" or Pal's crises are premonitory signs of more extensive, serious, and often fatal cerebrovascular disturbances that may follow if proper therapeutic measures are not imposed promptly. The serious and highly fatal cerebral hemorrhages or thromboses with cerebral infarction are comparable *to myocardial infarction in ischemic heart disease. When* carefully considered, the pathogenesis, clinical manifestations, prevention, treatment, and prognosis of ischemic cerebral disease and ischemic heart disease have much in common. *Why then, should the therapy for the two diseases* be so different? The disease in both organs is primarily *vascular (arterial)* disease. Neurodysfunction is secondary to ischemia, the clinical neurologic manifestations being merely reflections of cerebral ischemia or cerebral vascular insufficiency.

Since strokes are reflections of arterial disease, it is astonishing that those who are concerned most with establishing methods in therapy are not vascular or cardiovascular clinicians—i.e., physicians who are most expert in the behavior of the circulation in health and disease. Most neurologists, because of their knowledge of the functional anatomy of the brain, can localize ischemic and hemorrhagic lesions accurately, but they are generally not as much concerned with the behavior of the blood vessels and the circulation supplying *these nerve centers. This* is true of neurosurgeons as well.

Certainly many of the principles related to vascular disease of the limbs or of the myocardium apply to the brain. For example, *the cardiologist refrains from moving* a patient with a fresh myocardial infarct to the x-ray department to obtain even a simple chest film, but patients with cerebral infarcts are often flown to vascular centers, moved to x-ray departments and subjected *to* carotid artery puncture and *rapid injection of a bolus* or more of toxic and irritating contrast material in order to obtain a cerebral angiogram. Is this good management, or is the answer really known? Because strokes are known to be so highly fatal, when death does occur it is *easy to rationalize by saying, "Well, we did our best* and he died before we could have done any more."

Another aspect that deserves serious objective consideration is the influence of surgery applied to a patient with a fresh stroke. The cardiologist, for example, hesitates to subject his patient with a myocardial infarct to even minor surgery unless absolutely necessary, for he knows the stress of surgery and the high incidence of death or worsening of ischemic cardiac disease related to surgery. On the other hand, a patient with a stroke is often subjected not only to angiographic studies but even to complex cerebrovascular surgery. *The high rate of death from strokes and the stress of* surgery and conventional forms of medical therapy need careful evaluation.

However, is it necessary even today for the death rate from strokes to be so high? Might not this high mortality rate be a *reflection* of improper management? Surely, there is a need to try other principles in management of strokes based upon methods found to be of value in the medical management of ischemic heart disease. It must be accepted that the management of strokes is not ideal, but many patients with strokes are known to do fairly well if treatment is based upon medical principles well known in the *management of* peripheral vascular disease and heart disease. For example, the magnitude of the three-dimensional hemorrhage or infarct is often much smaller than the surrounding area of "concussion" or than that indicated by the magnitude of the functional disturbance. If the patient is kept alive, the extent of recovery is good and the residual scar is often astonishingly small. Furthermore, nature, by mechanisms unknown to man, can provide extremely good collateral circulation with ultimate marked or total regain of function or with little residual cerebral dysfunction.

It is appalling to see so little *effort directed toward the control* of blood pressure and factors responsible for sudden hazardous elevations in blood pressure such as physical and psychic stress, diet, sodium intake, excessive body weight, inadequate rest, *poor nursing, and smoking.* The use of vasodilators, sedation, controlled recreation, job placement, caffeine and alcohol intake, state of nutrition, vacations, electrolyte balance, chronic respiratory disease, oral hygiene, diabetes mellitus, thyroid disease, and erythrocytosis as well as the management of associated diseases, such as chronic infections, and many other factors associated with arteriosclerosis, aging, hypertension, and the like in the treatment of patients with strokes or in the prevention of strokes need careful study and evaluation. To say a patient is receiving or has received "medical therapy" fails to define the quality of medical care, especially preventive care. The

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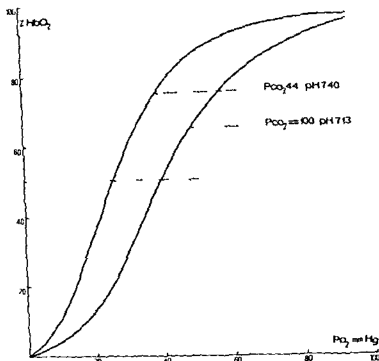


Fig. 1. Oxyhemoglobin dissociation curve obtained from a blood sample drawn from a subject after cardiac arrest. The right hand curve is the actual one obtained equilibrating with P_{CO_2} and pH levels present in vivo while the curve on the left was obtained under standard conditions.

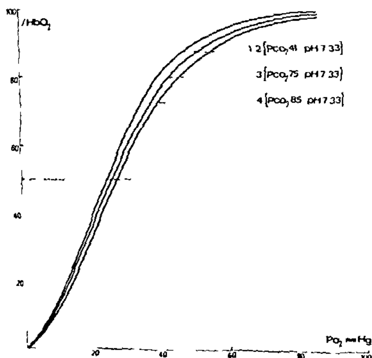


Fig. 2. Molecular effect of CO_2 on the oxyhemoglobin dissociation curve. Blood samples were drawn from a patient with chronic hypercapnia. Curves 1 and 2 were obtained equilibrating with 41 mm. Hg of P_{CO_2} and curves 3 and 4 with the P_{CO_2} level present in vivo in two consecutive days. The pH was adjusted to same level present in vivo.

nature of the medical therapy must be known in detail—i e not only what was advised but also what advice was precisely followed by the patient, and whether the advice that was given was ideal Because of difficulties in communication be tween doctor and patient, family or nurse or because of poor attitudes and lack of patience and time devoted to outlining management by the doctor with the patient or his family therapy is rarely followed precisely In fact, therapy is usually followed haphazardly and far from ideally

There is a need to evaluate and define precisely good therapy for stroke Certainly there is a need for a study of comparable cases in which the therapy advised and that followed are well known It is not sufficient to state that the treatment was surgical or medical Rather what actually was it? Who gave it how was it given and under what cir cumstances how extensive was the lesion were comparable groupings made for analysis and were many other important variables adequately identified and defined?

There is a great deal that can be done for ischemic brain disease There is no justification for a general fatalistic at titude in therapy However greater attention must be given to complete management based on knowledge of vascular *physiology and peculiarities of the cerebral circulation as* well as conditions related to the general state of health and neurology

It is known that cerebral arteries usually rupture when ar terial blood pressure is elevated even for brief periods. This is particularly true when the elevation occurs suddenly and to high levels, and especially if it involves the systolic pressure of a person with arteriosclerosis *Home recording* of blood pressure[3,4] not only can make it possible for the patient to follow antihypertensive therapy properly but it can also teach him to recognize those factors which elevate his blood pressure and those factors associated with lower pressure levels. He can then avoid the former factors and situations and favor the latter ones. Furthermore when his blood pressure rises, he can detect it early before a cerebrovascu lar accident can occur and immediately rest in bed and in stitute measures to reduce his blood pressure The important therapeutic aspects concerned with the rehabilitation and physiotherapy require careful planning since the patients with strokes so often have multiple diseases of considerable significance

Most cerebrovascular accidents are preventable if properly managed. The *prevention* of strokes cannot be over emphasized.

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The oxyhemoglobin dissociation curve in hypercapnic patients

A rightward shift in the oxyhemoglobin dissociation curve (OCD) mediated by 2 3 diphosphoglycerate appears to be a major adaptive response to congestive heart failure[1,2] and pulmonary insufficiency[3] Numerically the affinity with which hemoglobin binds oxygen is expressed by the P_{50} value which is defined as the partial pressure of oxygen at which 50 per cent of the hemoglobin is saturated with oxygen at pH 7 40 and 37 C However it has recently been emphasized that P_{50} values should be related to in vivo pH and not to a physiological pH of 7 40 as usually done[4] If this is true in diabetic ketoacidosis (as in the cases of Alberti and associ ates[4]) it is so much so in hypercapnia both acute and chronic It is well known, in fact, that CO_2 affects ox yhemoglobin dissociation also independently of the pH change[5-7] However the oxyhemoglobin dissociation curve of hypercapnic patients obtained maintaining the in vivo pH and P_{CO_2} values had not been studied so far For this pur pose we have developed a new technique which can give in a relatively short time P_{50} at P_{CO_2} levels found in vivo This was obtained by mixing in a variable ratio in an IL 237 tonometer the contents of two gas cylinders by means of two constant flow Brooks flowmeters containing CO_2 and a mix ture of O_2 and N_2 respectively In another tonometer P_{50} of the same blood sample was simultaneously measured under standard condition of 40 mm Hg of P_{CO_2}

Fig 1 shows the curves obtained from a blood sample drawn from a subject immediately after cardiac arrest. The leftward curve was obtained after equilibration with 44 mm Hg P_{CO_2} and the observed values of P_{O_2} were corrected to a standard plasma pH of 7 40[8] The value of P_{50} (26 mm Hg) does not differ from the normal The right hand curve was obtained equilibrating with same P_{CO_2} and pH levels as in vivo In this case a considerable increase of P_{50} (39 6 mm Hg) was observed.

Fig 2 refers to a chronic hypercapnic subject with par tially compensated respiratory acidosis Curve 4 was ob tained equilibrating with the P_{CO_2} level present in vivo (85 mm Hg) curve 1 was obtained equilibrating with 41 mm Hg of P_{CO_2} and adjusting the pH to the in vivo value by adding HCl On the following day the patient showed a P_{CO_2} of 75

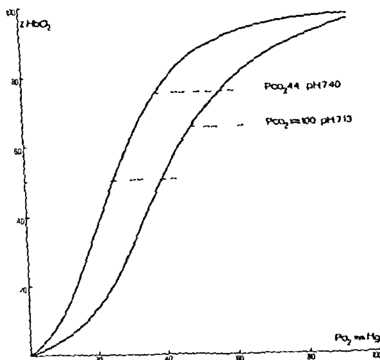


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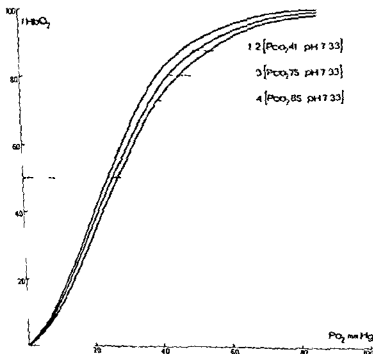


Fig. 2. Molecular effect of CO_2 on the oxyhemoglobin dissociation curve. Blood samples were drawn from a patient with chronic hypercapnia. Curves 1 and 2 were obtained equilibrating with 41 mm. Hg of P_{CO_2} and curves 3 and 4 with the P_{CO_2} level present in vivo in two consecutive days. The pH was adjusted to same level present in vivo.

mm Hg and the curve drawn by equilibrating with such a P_{CO_2} value (curve 3) was slightly more leftwards than the one on the previous day Besides the curve plotted by equilibrating with 41 mm Hg of P_{CO_2} and by adjusting the pH with HCl to same value as in vivo is exactly transferable on the curve obtained on the previous day (curve 2) Since the pH values are constant in the four curves the differences in their positions are due to a specific effect of molecular CO_2

The shift to the right of the ODC is finally useful so long as the arterial P_{O_2} levels do not drop below certain limits in fact if the arterial P_{O_2} value is very low as may occur in some acute situations (pulmonary edema etc) the oxygen exchanges take place in the lower part of the curve For this latter condition oxygen release to the tissues is paradoxically decreased by a displacement to the right of the curve suggesting another reason to correct acidosis in severe pulmonary edema or in cardiac arrest.

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Plasma uric acid and body weight

Recent years have seen the definition of many factors which can cause or contribute to an elevated level of plasma uric acid. It is well known for example that excess uric acid is produced in conditions with increased turnover of nucleic acids such as the myeloproliferative disorders or polycythemia rubra vera while in the Lesch Nyhan syndrome an x linked disease with certain characteristic neurological features there is excessive purine synthesis associated with a deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase[1] In addition to such metabolic abnormalities impaired excretion of uric acid can follow one of a multitude of causes such as the use of drugs acting on the renal tubule (pyrazinamide[2] or diuretics[3]) conditions producing lactic acidemia[4] ketosis with beta hydroxybutyric acidemia,[5] and many others

Apart from such situations where we now have reasonably clear ideas about some of the biochemical processes involved there are other associations of hyperuricemia in which the mechanisms are not at all well understood. As well as age and sex variations in uric acid levels ethnic differences have been found a number of indigenous Pacific peoples have mean plasma urate levels significantly above those of Caucasians[6] An intriguing correlation borne out by several studies is that observed between uric acid levels and intelligence particularly as judged from the findings among university professors[7] and business executives[8] with regard to drive achievement range of activities and leadership Another firmly established association is between uric acid and plasma lipids. hyperuricemia is common among patients with hypertriglyceridemia[9] and patients with gout have significantly higher mean levels of triglyceride and of free fatty acids but not of cholesterol than control subjects.[10] About 25 per cent of hypertensives are found to have a raised plasma urate[11 12] quite aside from the added effects of treatment or of co existent renal disease *Hyperuricemia here* may be due to a selective impairment of tubular secretion The age old belief that gout is often associated *with overin*dulgence in alcohol has acquired some scientific corroboration by the finding of sufficient hyperlacticacidemia during alcoholic intoxication to suppress uric acid *excretion*[13] *while* there is evidence that long term consumption of alcohol may in some way lead to hyperuricemia with overproduction of *uric acid.*[14] *Correlations* have also been found between levels of uric acid and hemoglobin[15] and plasma proteins[16]

The problem of uric acid and vascular disease remains to be *clarified* Reports of hyperuricemia associated with myocardial infarction[17 19] must be treated with caution, because this situation does not readily lend itself to adequately controlled studies and the influences of such factors as drug treatment and changes in body fluid com[illegible]

are difficult to assess. A relation between hyperuricemia and atheroma has been suggested in the past,[20-22] but this has not been borne out by clinical experience.[23,24] In the Framingham survey[25] a relationship was found between the occurrence of gouty arthritis and signs of coronary artery disease but on removal of patients with gout from the analysis any association between coronary disease and hyperuricemia was no longer apparent. A possible link between gout and diabetes mellitus or abnormal glucose tolerance has also been suggested,[26-28] but is not confirmed by epidemiological studies.[29,30] Blood sugar levels after a glucose load and in the fasting state are higher in gout patients than in controls of normal body weight, but such differences are not evident when weight matched controls are taken.[31]

One of the most constant relations of this type is between plasma levels of uric acid and body weight surface area or body bulk, corrected for stature expressed as the ponderal index (height divided by cube root of weight) this has been a feature of nearly all the epidemiological surveys which have investigated the problem.[16,25,32-34] Clinical studies, too indicate that the sufferer from gout tends to be overweight[24] although there are many individual exceptions. Thus, as Acheson and Chan[35] have pointed out, the associates of a high uric acid are the associates of plenty but we do not yet know the exact nature of relationships between urate levels and such factors as obesity surface area intelligence drive blood pressure diet alcohol consumption, and hemoglobin, many of which have their own complex interrelationships. Some of these factors are variables, alterations of which might bring about changes in plasma levels of uric acid. Of course thinking in the other direction, uric acid is itself a variable which nowadays can be easily regulated—do we conceivably deprive a gouty patient of his drive or intelligence when we lower his uric acid level? Which comes first the gouty hen or the high cholesterol egg? Or are most of these relationships not directly causal?

In a recent investigation into the possible effect of weight change, plasma and urinary uric acid levels were estimated (on a low purine diet) before and after a period of weight reduction in 15 subjects.[36] Weight loss ranged from 4 to 22 kilograms (mean 8 kilograms) representing a fall of between 4 per cent and 18 per cent (mean 8 per cent) of initial body weight. Plasma urate levels fell in 12 of the 15 subjects the mean fall (0 8 mg /100 ml) being significant as was the relation between degrees of weight loss and fall in plasma uric acid. By contrast changes in urinary uric acid were not constant, and although the four subjects with the highest initial values demonstrated a fall in urinary uric acid after weight loss, the over all mean reduction was not significant.

It therefore appears that an individual's plasma uric acid is influenced to some extent by his weight, and that this is responsible for the observed association between the two variables. The mechanism of the association remains uncertain and it is not clear to what extent metabolic or renal factors, or a combination of both, are operating. Proportions of body water may be relevant a heavy subject has a larger absolute quantity of body water than a lighter person of identical age and sex, but it makes up a smaller proportion of the total body weight. In other words weight loss is accompanied by relative hydration, and such a dilutional effect may be at least a partial explanation of the fall in plasma uric acid.

The adverse influence of obesity on good health and longevity is generally accepted. The prospect of a slight fall in plasma uric acid, with perhaps a diminished susceptibility to gout may serve as an added, though minor inducement to persuading our obese patients to lose weight.

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Observations on papillary muscle dysfunction

Papillary muscle dysfunction is now recognized as a common accompaniment of coronary artery disease Burch and associates[1] originally described this syndrome in 1963 and emphasized that the characteristic murmur was late in systole often with an ejection or diamond shaped configuration Subsequent workers have found that the murmur may vary in timing from early to late systole or may even be holosystolic[2,3] There is now general agreement about the variability of the murmur in this entity However two other findings are controversial

1 The presence of a late systolic click has been stressed as a common finding by various workers[4,5] and not mentioned by others[3]
2 A very loud first heart sound has been described as a clinical feature which characterizes the entity[2]

We recently have recorded phonocardiographically findings in two patients with an *acute myocardial infarction* which can throw additional light on this controversy

A 54 year old man was admitted to Misericordia Hospital with a history of severe chest pain The electrocardiogram revealed an acute inferior wall myocardial infarction and the serum enzymes were compatible with the diagnosis A loud pre systolic gallop was heard on admission and the first heart sound was diminished in intensity No murmur was heard On the fourth hospital day a booming first heart sound was heard with no associated heart murmur At this time the patient was not febrile or anemic and his cardiac rate was only 85 beats per minute A phonocardiogram was taken which

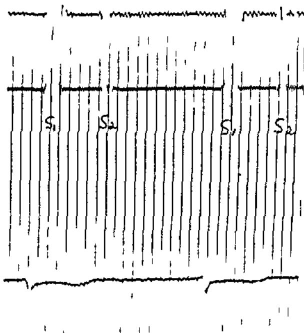


Fig 1 Phonocardiogram of 54 year old man patient with posterolateral myocardial infarction Note the booming first heart sound (S_1)

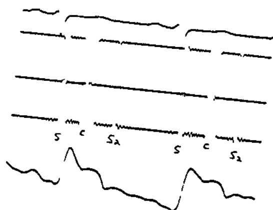


Fig 2 Phonocardiogram of 58 year-old man patient with acute anterolateral wall myocardial infarction Note the prominent first heart sound (S_1) the holosystolic apical murmur and the prominent click (*C*)

documented the finding (Fig 1) The loud first heart sound persisted for the rest of his hospital stay On the seventh hospital day he developed a fatal cardiac arrest. At autopsy a posterolateral myocardial infarction was found The posterior papillary muscle was necrotic without evidence of rupture Thus a loud first sound can indeed occur in papillary muscle dysfunction, and may not even be accompanied by a systolic murmur

A 58 year-old man was admitted to Misericordia Hospital with a history of crushing chest pain. The electrocardiogram revealed an acute anterolateral wall myocardial infarction, and the serum enzymes corroborated this diagnosis. On admission a presystolic gallop was heard with a faint first heart sound. On the fourth hospital day a prominent first heart sound as well as a holosystolic apical murmur were heard. On the thirteenth hospital day a very loud midsystolic click was also heard. A phonocardiogram was obtained which documented this finding (Fig 2) Five days later the click disappeared while the murmur persisted. The patient was eventually discharged from the hospital Thus a systolic click can indeed occur *de novo*, during the course of an acute myocardial infarction, and is part of the spectrum of papillary muscle dysfunction.

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Book reviews

Complete Transposition of the Great Arteries. By Reda M Shaher MB ChB MRCPE Ph.D New York 1973 Academic Press Inc 550 pages Price $32 00

This is a 500 page volume on one relatively rare congenital defect. Surely the patient with it would be most concerned with its many problems. Nevertheless Dr Shaher has thoroughly and masterly reviewed the problem of complete transposition of the great arteries The monograph includes a discussion of embryology anatomy classification and definition, incidence etiology clinical manifestations, angiocardiography roentgenography and treatment. This is a thorough consideration of complete transposition of the great arteries It certainly should interest all cardiologists and cardiac surgeons. This is a very good and highly recommended book.

The Cardiac Arrhythmias ed. 2 By Brendan Phibbs, MD FACP FACC St. Louis 1973 The C V Mosby Company 205 pages Price $7 50

This second edition of The cardiac arrhythmias has been brought up to date to include cardiac pacing resuscitation and other advancements in cardiology pertaining to arrhythmias The book is simple and clear It is a paper back The illustrations are good and the presentations are from a practical clinical point of view Dr Phibbs has continued to correlate the clinical problems with the arrhythmias The presentation is for training in cardiology mainly with the use of questions and answers Beginners will find this to be a useful small book

The Ductus Arteriosus By Donald E Cassels MD Springfield Ill 1973 Charles C Thomas Publisher 345 pages Price $17 75

This monograph on the ductus arteriosus includes a rather thorough review of this anatomic structure with the main objective concerned with a congenitally patent ductus As would be expected the author reviews the anatomy embryology mechanisms of normal closure at birth and possible causes for postnatal patency the clinical problems and manifestations of a patent ductus and its management. This is a good review of the subject. The illustrations are good and the text well written Students, residents cardiologists cardiac surgeons, and physiologists will find this to be a very useful book A patent ductus arteriosus is one of the few congenital cardiac defects that can be surgically completely cured. Therefore clinicians should always recognize it to institute a surgical cure

The Inflammatory Process ed. 2 vol 2 Edited by Benjamin W Zweifach MD Lester Grant MD and Robert T Mc Cluskey MD New York 1973 Academic Press Inc 419 pages Price $28 00

This second edition of The inflammatory process is on an extremely important subject. Every human being experiences an inflammatory type of illness or lesion many times during his lifetime Yet the phenomenom is poorly understood. Volume 2 is a good review of present concepts on the subject The 11 chapters are concerned with microvascular aspects of tissue injury capillary permeability rheology the lymphatic system sticking and emigration of white blood cells, chemical mediators homeostasis, and thrombosis The contributors are experts in their respective fields. The extensive use of electron microscopy in recent investigations is realized from the many illustrations and studies discussed The discussions incidentally are concise and readily understood by beginners in the field of the microcirculation This reviewer is still impressed with the extent of the gaps in knowledge concerning inflammation The inflammatory process is initiated by many factors yet the final manifestations are remarkably common. This is an excellent and valuable publication which should interest pathologists physiologists, and clinicians

Books received

LIFE IS FOR LIVING HOW YOU CAN MAKE IT ALONE. By Theresa A Horse New York, 1973 Doubleday & Company Inc New York, 131 pages. Price $4 95

METABOLISCHE UND HAMODYNAMISCHE TRAININGSEFFEKTE BEIM NORMALER UND GESTORTER MUSKELDURCHBLUTUNG Edited by Dr M. Kohler and Dr W Schoop Stuttgart, 1973 Verlag Hans Huber Bern, 88 pages. Price $9 50

HERZSCHLAGFREQUENZ UND LEISTUNG Edited by Fritz Ludwig Schmidt, Basel, 1973 S Karger AG 123 pages. Price $9 30

CARDIOVASCULAR DISEASES, Vol. 28 By Kalman Greenspan Ph.D., and John Fischer M D Flushing 1973 Medical Examination Publishing Company 168 pages.

Seminar on cardiovascular epidemiology

The Council on Epidemiology and Prevention of the International Society of Cardiology will hold its seventh ten day International Teaching Seminar on Cardiovascular Epidemiology in Hungary on Aug 4 through 16 1974 Approximately 30 Fellows can be accepted Final selection will be made by the Council s Seminar Committee Nominees should be at the postdoctoral level with some residency training or its equivalent Limited funds may be available to pay for room and board during the seminar and to give partial assistance with travel costs. *Fluency in English is an absolute essential* Three documents are required for application a letter of nomination from the chief of the department or institution of the nominee a personal letter of application from the nominee and the applicant s curriculum vitae These should be sent before May 1 1974 (the deadline) to Jeremiah Stamler M D Secretary of the Council on Epidemiology and Prevention I.S.C Room 9 105 Ward Building Northwestern University Medical School 303 E. Chicago Ave Chicago Ill 60611

Advancement of tension control

The first meeting of the American Association for the Advancement of Tension Control will be held in Chicago Ill on Oct. 12 1974 The Association includes the following six divisions dentistry education medicine physical therapy psychology and members at large For information about membership and the meeting write to the Executive Office P O Box 7512 Roanoke Va 24019 attention Dr Robert Rinehart

Diagnostic ultrasound

The third biannual diagnostic ultrasound seminar will be held on June 6 and 7 1974 at the Philadelphia Marriott Motor Hotel Philadelphia Pa., sponsored by Episcopal Hospital and Temple University Health Sciences Center Seminar presentations and demonstrations will embrace all four types of information display used in ultrasound diagnosis. The tuition fee is $80 00 for physicians and $40 00 for residents, technicians, and nurses both fees include luncheons. The faculty for the seminar includes Drs. William Asher D Jackson Coleman Barry B Goldberg Raymond Gramiak, Donald King Morris Kotler Marc Lapayowker Gordon Perlmutter Howard Pollack Renate Soulen Horace Thompson and Marvin Ziskin. For further information write to Barry B Goldberg M D Head, Section of Diagnostic Ultrasound Department of Radiology Episcopal Hospital Front St & Lehigh Ave Philadelphia Pa. 19125

Conference on clinical aspects of cardiovascular disease

Symposia Medica Foundation presents an international conference on Clinical Aspects of Cardiovascular Disease to be held in London England, from May 17 through May 25 1974 For further information please write Ms. Cynthia Soika M A Projects Director Symposia Medica Foundation, 305 E 24th St. New York, N Y 10010 Telephone (212) 686 2364

American Heart Journal

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Editorial

Toxic agents, cardiovascular disease, and the polluted home

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The present surge of interest in pollution is concerned with the outside environment. This fact is extremely interesting and perplexing when it is realized that one of the mo t polluted environments is *inside* the American home A home of smoking people is forever polluted with tobacco smoke which is breathed and rebreathed even during sleep Insecticides and insect repellents, toxic enough to kill a bug and certainly toxic enough to injure cells of man are frequently sprayed throughout the home These agents certainly are not good for any living cells of man Sprays for mosquito control, roach killing agents, and other insecticides pollute the air of the closed home that is breathed throughout the night and day Then of course there are also the deodorant sprays The users know not what they contain but only that they smell clean and pleasant Add to these the antiseptic agents that are used freely All are extremely toxic substances There are also the home remedies for belief that they do the family no harm and without the realization that some people are supersensitive to many agents Then there are the cosmetics hair sprays and body cleaners the phenolic clean smelling vaginal douches that are used freely All are extremely toxic substances There are also the home remedies for headache dyspepsia insomnia anorexia weight control constipation and depression nutrition supplements, and skin bracers and sun taners, as well as furniture polishes cleaning agents and detergents to mention a few of the many potentially toxic substances brought into the home

It is amazing how tough the human body is to survive this type of constant unrelenting chemical trauma But all people are not so tough or resistant In fact with careful history taking it is evident that many patients with vasculitis lupus erythematosus disseminatus and related "collagen diseases or autoimmune diseases seem to have their illnesses initiated and perpetrated by some of these pollutants especially the phenolic compounds The relationship of cardiovascular disease to these agents is impressive from my own clinical observations Surely the use of these substances do the health of man no good. The polluted home needs attention It is folly to improve only the outside environment of man while no effort is made to improve the environment inside the home In fact, with advertising and sales claims and other sales efforts the inside of the home is being increasingly polluted Some of these toxic agents injure the cardiovascular and renal systems as well as other cells both indirectly and directly

May the polluted American home receive serious attention There must be other less hazardous methods for controlling and managing the problems related to the home than those

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presently used In the everyday practice of preventive medicine all toxic agents should be removed from the environment of people Remember the possible etiologic relationships of toxic agents to hypersensitivity states with resultant vasculitis and so called "autoimmune disease Surely, no harm is done if *all* toxic agents are removed from patients with these diseases of unknown etiology Remember, although some people *seem* to tolerate toxic agents, hypersensitive people will not. Most people can eat strawberries, but a person hypersensitive to the fruit need only eat one to develop severe urticaria No one knows or even makes a serious effort to test people for sensitivity to the many pollutants extensively displayed inside the home and that are touched, swallowed, or breathed and rebreathed throughout the day and night.

Echocardiographic interventricular septal wall motion and thickness A study in health and disease

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The interventricular septum forms an integral part of both right and left ventricles and is under the effects of pressure and volume from each ventricle simultaneously Prior to the development of echocardiography there has been no satisfactory noninvasive technique for studying the motion of the interventricular septum in human beings Although septal thickness can be determined by biplane angiography the application of a noninvasive technique to study both the thickness and motion of the interventricular septum is highly desirable

Echocardiography has now become an established, noninvasive procedure in the assessment of ventricular function and anatomy[1-7] Echoes from the interventricular septum were originally identified by Edler and co workers[8] and were later utilized in the study of right and left ventricular size[9] Diamond and co workers[10] have demonstrated the usefulness of septal echoes in the identification of patients with atrial septal defect and Abbasi and co workers[3] and Henry Clark and Epstein[4] have identified a characteristic echocardiographic septal abnormality in patients with idiopathic hypertrophic subaortic stenosis (hypertrophic cardiomyopathy)

The present study was designed to explore the potential use of this technique in evaluating the pattern of motion and thickness of the interventricular septum in normal subjects and in patients with various cardiovascular diseases

Methods

The study consisted of a group of 20 normal volunteer subjects free of any evidence of heart disease aged 20 to 40 years 5 normal subjects who have no hemodynamic or angiographic evidence of heart disease and a group of 43 patients aged 16 to 67 years with various forms of cardiovascular diseases proved at cardiac catheterization

Eleven patients had volume overload of the left ventricle (one with patent ductus arteriosus two with isolated mitral regurgitation two with aortic regurgitation and the rest had mixed aortic and mitral regurgitant lesions) Two patients had pressure overload of the left ventricle (one with isolated aortic stenosis and one had long standing systemic hypertension) There were 10 patients with coronary atherosclerotic heart disease seven of whom had evidence of left ventricular dysfunction as judged by reduced ejection fraction on angiography and/or the presence of various forms of asynergy Five patients had congestive cardiomyopathy four patients had idiopathic hypertrophic subaortic stenosis (IHSS) and five patients had mitral stenosis with a calculated valve area of 1 2 cm² or less There were four patients with atrial septal defect and two others with ventricular septal defect. In eight other patients and six volunteer subjects not included in the study clear simultaneous identification of both septal surfaces as well as the posterior wall endocardial surface was not

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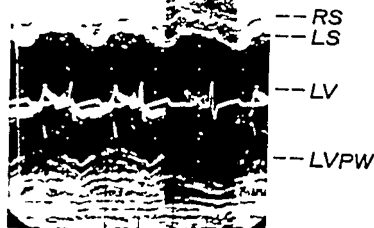


Fig 1 Echocardiogram of a patient (J M) with mitral regurgitation demonstrating the use of different attenuation controls to obtain clear septal outlines. LS = left side of the septum RS = right side of the septum LV = left ventricular cavity LVPW = left ventricular posterior wall

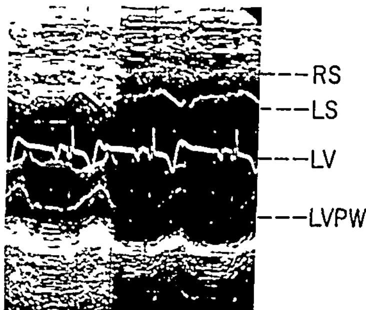


Fig 2 Echocardiogram with normal septal motion and thickness (8 5 mm) in a normal subject (S K)

possible The 43 patients and the 25 normal subjects with good quality echocardiograms will form the material for this report

All cardiac echograms were recorded by the Unirad 100 series echocardiographic diagnostic system, utilizing a 2 5 mega Herz lead Zicronate transducer, 0 75 inches in diameter and a frequency of 1,000 pulses per second With the patient in the recumbent position and slightly tilted to the left side, the transducer was applied in the fourth and fifth intercostal space near the left sternal edge pointing slightly laterally and inferiorly The mitral valve echo was initially identified by rotating the transducer slightly medially, then with slight movement laterally, and caudally the posterior ventricular wall was identified by its characteristic motion [9,11] With slight additional adjustment of the transducer to include echoes from anterior and posterior mitral leaflets, both surfaces of the interventricular septum were simultaneously identified by their characteristic motion of almost two parallel lines representing the right and left ventricular septal endocardial surfaces (Fig 1) The A (depth intensity) mode was utilized to identify cardiac structures and the M (time motion) mode was used to obtain permanent Polaroid photographs. The reject control was usually set at maximum to eliminate low density echoes Sensitivity for display of near field structures was adjusted by using the depth compensation control Attenuation of 10 decibels or more provided different gain settings (Figs 1 and 3) Measurements were made at end diastole corresponding to the R wave of the simultaneously recorded electrocardiogram to include the distances between the right and left ventricular surfaces of the interventricular septum The measurements were done independently by two of the authors The variation between the two observers (maximal variation 3 to 5 mm) was not statistically significant with a P value >0 5 between their mean values In the normal (N) type of septal motion the left ventricular septal surface moves posteriorly with the onset of ventricular ejection concurrently with a synchronous anterior motion of the endocardial surface of the left ventricular posterior wall [10] In type A motion, both the left ventricular septal surface and the endocardial surface of the left ventricular posterior wall move anteriorly during ventricular ejection [10] In type B motion the septal echoes are flattened during systolic ventricular ejection, with an asynchronous slightly posterior motion during early ventricular diastole Occasionally patients have a type of abnormal septal motion that appears to be a hybrid to type A and type B

The type of septal motion determined by echocardiography was compared with other indices of ventricular function and anatomy determined by cardiac catheterization, including the calculated left ventricular ejection fraction and the study of left ventricular wall motion Coro

Table I Catheterization diagnosis and echocardiographic data in 43 patients

Patient's initial	*Age (yr) and sex*	*Diagnosis*	*Septal motion type*	*Septal thickness (mm.)*
P C	26 F	Patent ductus arteriosus	Normal	10 0
F M	63 M	MR (ruptured chordae)	Normal	9 2
J M	42 F	MR	Normal	8 5
B E	63 M	MR, AR	Normal	10 2
M. R	34 F	MR, AR	Normal	10 6
H R	25 M	AR	Normal	11 2
F S	26 M	AR VSD	Hybrid	11 0
J N	62 F	MR, AR	Normal	8 3
B O	39 F	MR, AR MS	Normal	10 2
M W	38 F	AR, AS	Normal	10 5
B D	29 F	AR MR, MS TR	Normal	11 5
C H	36 M	AS	Normal	13 3
W J	65 F	Systemic hypertension	Normal	10 2
J M	27 M	MS	Normal	8 2
F B	57 M	MS	Normal	7 8
D J	33 F	MS	Type B	6 5
A. H	39 F	MS	Normal	6 0
H. L	32 M	MS	Normal	7 0
W P	57 M	CAHD	Type B	8 1
H. S	51 M	CAHD	Normal	8 2
C P	43 M	CAHD	Normal	8 3
S B	61 M	CAHD with LV dysfunction	Type B	10 4
L. L	67 F	CAHD AR, and LV dysfunction	Type B	10 0
P P	57 F	CAHD with LV dysfunction	Type B	9 3
E. J	50 M	CAHD with LV dysfunction	Normal	9 6
C K	52 M	CAHD with LV dysfunction	Type A	11 2
H C	46 M	CAHD with LV dysfunction	Type B	10 4
A H	46 M	CAHD with LV dysfunction	Normal	5 7
B G	46 M	Cardiomyopathy	Normal	7 8
B J	26 M	Cardiomyopathy	Type B	10 0
T C	60 M	Cardiomyopathy	Normal	9 3
W J	44 M	Cardiomyopathy	Type B	9 2
J H	42 M	Cardiomyopathy	Type B	9 0
J B	52 M	IHSS	Normal	21 3
W M	24 M	IHSS	Normal	16 0
S. M	23 M	IHSS	Normal	15 8
H M	44 M	IHSS	Normal	18 4
J B	41 M	ASD	Type B	12 5
D J	31 F	ASD	Type B	12 0
G A.	19 F	ASD	Type A	11 0
E H	55 M	ASD	Type A	10 5
G B	26 F	VSD	Normal	8 5
B T	17 M	VSD	Normal	14 0

Abbreviations AR Aortic regurgitation AS Aortic st n is ASD Atrial septal defect CAHD Coronary athero clerotic heart disease IHSS Idi p thic hypertroph c subaortic stenosis LV Left ventricle MR Mitr l regurgitation MS Mitral stenosis TR Tricusp d r gurgitation VSD Ventricle septal defect

nary arteriography was performed by the Judkins technique.[11]

Results

Table I lists the diagnoses and the echocardiographic data of the 43 patients The 25 normal subjects all had a normal ventricular septal wall motion with a mean septal thickness of 7 2 mm. ± 0 7 S D Fig 2 shows the characteristic pattern encountered in normal subjects

The 11 patients with left ventricular volume overload had increased thickness averaging 10 1 mm ± 1 0 S D (range 8 5 to 11 2 mm.) The pattern of motion was normal in all except one pa

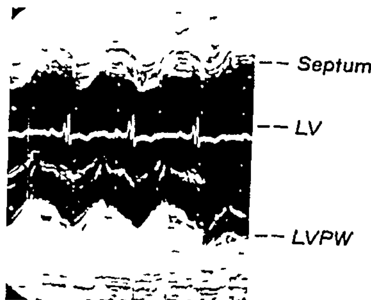


Fig 3 Echocardiogram from a patient (F S) with volume overload and left ventricular dysfunction showing abnormal septal motion The movement of the left ventricular septal surface appears to be a hybrid of types A and B

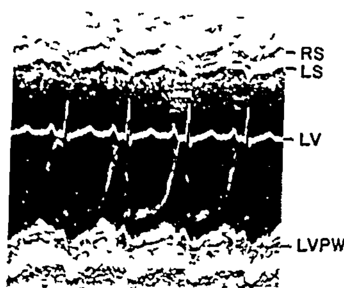


Fig 4 Echocardiographic tracing from a patient (C K) with CAHD left ventricular dysfunction and reduced ejection fraction by angiography showing asynchronous motion of the septum

tient (F S) who exhibited abnormal septal motion (Fig 3) This patient had a ventricular septal defect, severe aortic regurgitation, and myocardial dysfunction The two patients with isolated pressure overload of the left ventricle both exhibited normal motion but increased thickness (mean 12 2 mm)

The five patients with mitral stenosis all had a septal thickness within the normal range (7 0 to 8 2 mm) with a mean of 7 1 mm ± 0 9 S D This was not statistically different from the normal group Four patients had a pattern of normal septal motion while one had type B pattern of motion

The 10 patients with coronary atherosclerotic heart disease, seven of whom had evidence of left ventricular dysfunction, had an increased septal wall thickness (mean 9 2 mm ± 1 0 S D, range 8 1 to 11 2 mm) Six of those patients had normal septal motion and three had type B motion and one had type A motion (Fig 4)

The five patients with congestive cardiomyopathy had an increased septal wall thickness of 9 1 mm ± 0 8 S D Three of these patients had type B motion, and in the other two patients septal motion was normal The four patients with IHSS all had normal septal motion (Fig 5) but the striking increase in septal thickness of 17 8 mm (average 15 8 to 21 3 mm) which clearly separated them from all other groups

Of the four patients with atrial septal defect



Fig 5 Echocardiogram from a patient (S M) with IHSS showing marked asymmetric hypertrophy of the septum.

two had type A motion (Fig 6), and two had type B motion One of the latter also had anomalous pulmonary venous drainage and a markedly dilated pulmonary artery The average septal thickness of the four patients with atrial septal defect was significantly increased (mean 11 5 mm ± 0 9 S D, range 10 5 to 12 5 mm) Both of the patients with ventricular septal defect showed normal septal motion and one of them (B T) had an increased thickness of 14 0 mm Fig 7 depicts the septal wall thickness in the main groups of subjects

Relation of the septal wall motion to angiographic ejection fraction pattern of ventricular contraction and coronary cineangiography Of the 36 patients without cardiac shunts, 27 had high quality cineangiograms for the accurate calculation of ejection fraction and study of ventricular wall motion Four of the

five normal subjects with normal cardiac catheterization data also had satisfactory left ventricular cineangiograms Table II compares the echocardiographic pattern of septal motions with various functional and anatomic indices All five subjects with normal cardiac catheterization and normal septal motion had a calculated ejection fraction between 0 58 and 0 73 In the 10 patients with valvular heart disease nine had normal septal motion while the ejection fraction ranged between 0 46 and 0 61 and three had various degrees of hypokinesis The one patient with type B motion had an ejection fraction of 0 46

Of the nine patients with coronary atherosclerotic heart disease five had normal septal motion with an ejection fraction ranging from 0 21 to 0 55 and four of these had angiographic evidence of some degree of left ventricular hypokinesis The three patients with asynchronous type B motion had ejection fractions from 0 24 to 0 59 and all three patients had at least some degree of left ventricular hypokinesis One patient (C K) had a left bundle branch block pattern and one patient (W P) had a left anterior hemiblock Three of the four patients with cardiomyopathy had type B motion and depressed left ventricular ejection fractions (range 0 26 to 0 42) and diffuse left ventricular hypokinesis One of these patients (J H) had left bundle branch block on the electrocardiogram. All four patients with idiopathic hypertrophic aortic stenosis had normal or elevated ejection fractions (range 0 65 to 0 86)

Discussion

Criteria for the identification of cardiac echoes has been extensively reviewed in the literature [13] Identification of the septal echoes is usually relatively easy and reproducible if care is taken in directing the transducer [4,9,13] When the latter is oriented more toward the apex septal motion is usually exaggerated. On the other hand, when the transducer is directed more cephalad toward the aortic root the septal echoes blend into those from the posterior aortic wall giving the appearance of paradoxical motion This error can be avoided by simultaneous identification of the septum with both anterior and posterior mitral leaflets. In general, clear indentification of the right ventricular surface of the septum is more difficult because of its proximity to the right

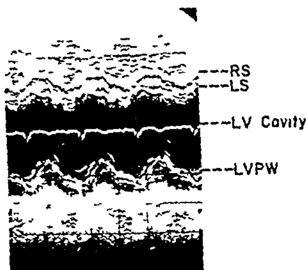


Fig 6 Echocardiogram reveals abnormal type A septal motion in a patient (E. H) with atrial septal defect.

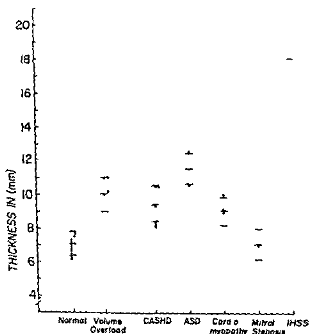


Fig 7 Mean values ± S.D of the septal wall thickness in control subjects and patients

ventricular wall, and because the right septal surface can produce as multiple echoes, rather than as a single clear surface Our overall failure rate was 18 per cent in obtaining satisfactory echocardiographic recordings of the interventricular septum. In this study almost all of the patients with cardiovascular disease except those with mitral stenosis, had abnormal interventricular septa (Fig 7)

Patients with increased ventricular stroke

Table II Comparison of echocardiographic septal motion with ventricular function and anatomy

Patient's initial Age (yr) and sex	*Diagnosis*	*Type of septal motion*	*Ejection fraction (angiography)*	*Coronary angiography*	*Ventricular wall motion (angiography)*
F M 63 M	Ruptured chordae	Normal	0.58	Normal	Normal
B E 63 M	MR AR	Normal	0.50	50% occ of RCA	Moderate hypokinesis
M R 34 F	MR AR	Normal	0.61	Normal	Normal
H R 25 M	AR	Normal	0.48	Not done	Mild hypokinesis
B O 39 F	MR AR MS	Normal	0.51	Normal	Normal
M W 38 F	AR AS	Normal	0.57	Normal	Normal
C H 36 M	AS	Normal	0.53	Normal	Normal
J M 27 M	MS	Normal	0.50	Not done	Normal
D J 33 F	MS	Type B	0.46	Not done	Mild hypokinesis
A H 39 F	MS	Normal	0.53	Normal	Normal
W P 57 M	CAHD	Type B	0.40	75% occ LAD & LCM	Mild hypokinesis
S B 61 M	CAHD	Type B	0.24	Comp occ LAD	LV apical aneurysm
P P 57 F	CAHD	Normal	0.43	75% occ of LAD	Akinetic apex diffuse hypokinesis
E J 50 M	CAHD	Type B	0.59	90% occ of prox. LCA mult occ RCA	Asynergesis of apex
H C 46 M	CAHD	Normal	0.45	90% occ LCA	Diffuse hypokinesis
A H 46 M	CAHD	Normal	0.55	80% occ RCA	Akinetic apex
C P 43 M	CAHD	Normal	0.37	50% occ RCA LCM	Normal
H S 51 M	CAHD	Normal	0.21	80% occ LCA	Apical hypokinesis
C K 52 M	CAHD	Type A	0.37	Diffuse obst. RCA	Hypokinesis
W J 44 M	Cardiomyopathy	Type B	0.38	80% occ LAD	Mild hypokinesis
B J 26 M	Cardiomyopathy	Type B	0.42	Normal	Diffuse hypokinesis
J H 42 M	Cardiomyopathy	Type B	0.26	Normal	Hypokinesis
B G 46 M	Cardiomyopathy	Normal	0.40	30% occ RCA	Severe hypokinesis
J B 52 M	IHSS	Normal	0.65	Normal	Severe hypokinesis
W M 24 M	IHSS	Normal	0.86	Normal	Normal
S M 23 M	IHSS	Normal	0.72	Normal	Hyperkinesis (diffuse)
J B 44 M	IHSS	Normal	0.68	Normal	Hyperkinetic apex
G S 54 F	Normal cath	Normal	0.73	Normal	Normal
C S 43 F	Normal cath	Normal	0.61	Normal	Normal
C E 43 F	Normal cath	Normal	0.58	Normal	Normal
V L 62 F	Normal cath	Normal	0.69	Normal	Normal

Abbreviations Comp Complete IHSS Idiopathic hypertrophic subaortic stenosis LAD Left anterior descending LCA Left main coronary artery LCM Left circumflex LV Left ventricle Obst Obstruction Occ. Occlusion Mult Multiple RCA Right coronary artery

work may have increased total left ventricular mass from either increased pressure work or volume work [14,15] Feigenbaum and co workers[11] found good correlation between echocardio graphic measurements of left ventricular wall thickness and findings at surgery or autopsy Troy, Pombo, and Rackley[16] also demonstrated a good correlation between echocardiography and angiocardiography in the determination of left ventricular thickness and mass In our study, pa tients with either increased pressure or in creased volume overload had a consistent in crease in septal wall thickness Asymmetric sep tal hypertrophy by echocardiography has been found quite specific for identifying patients with IHSS, even before obstruction is present [3,4] The septal thickness in four patients with IHSS was distinctly higher than that in any other patients studied

Septal motion has been reported to be abnor mal in patients with atrial septal defect, anom alous pulmonary venous drainage or tricus pid regurgitation [10,17] In types A or B abnormal septal motion, the ventricular septum moves out of phase with the posterior left ventricular wall In patients with right ventricular volume over loading Diamond and co workers[10] suggested that the abnormal septal motion was due to the right ventricle having a stroke volume greater than the left, with the septum contributing

relatively more to right ventricular ejection Meyer and co workers[17] showed that the abnormal motion reversed to normal in most of the patients after surgical repair They proposed that the abnormal septal motion was due to a pronounced anterior motion of the entire heart secondary to a dilated right ventricle Septal motion has not been studied systematically in patients with left ventricular disease Since the septum contributes significantly to left ventricular ejection it is likely that echocardiography might demonstrate abnormal modes of septal contraction similar to those commonly found by angiography in patients with ventricular dysfunction Although many patients with left ventricular mechanical dysfunction did have abnormal septal motion demonstrated, this was not always found and a significant number of such patients had normal septal motion Five out of nine patients with significant coronary atherosclerotic heart disease and one out of four patients with cardiomyopathy exhibited normal septal motion Four of the coronary atherosclerotic heart disease patients with abnormal septal motion all had significant involvement of the left anterior descending coronary artery The contribution of bundle branch block or fascicular block observed to altered septal motion needs further investigation In a group of patients with acute myocardial infarction Inoue and co workers[18] demonstrated consistent echocardiographic abnormalities of the posterior left ventricular wall velocity and excursion Similar sensitive measurements of septal motion are subject to error since the amplitude of motion can be altered by minor changes in the position and orientation of the transducer although the general pattern of motion is more easily produced.

The data in the present study would suggest that the finding of an abnormal septal motion in patients with coronary atherosclerotic heart disease is strongly suggestive of associated left ventricular dysfunction On the other hand, the converse is not necessarily true and patients with coronary atherosclerotic heart disease and significant left ventricular dysfunction may have normal septal motion. Abnormalities of septal motion are common in patients with a wide variety of other types of heart disease particularly atrial septal defect and congestive cardiomyopathy Abnormalities of septal thickness was common in all varieties of heart disease studied and was extreme in patients with IHSS

Summary

The interventricular septal wall thickness and motion was studied by echocardiography in 25 normal subjects and 43 patients with various cardiovascular disease proved at cardiac catheterization The mean septal thickness was 7 2 mm. ± 0 7 S D in the normal subjects, 10 1 mm ± 1 0 S D in 11 patients with left ventricular volume overload (P < 0 01) and a mean of 12 2 mm in two patients with pure pressure overload of the left ventricle Ten patients with coronary atherosclerotic heart disease (CAHD) had an average septal thickness of 9 2 mm ± 1 1 S D and in five patients with congestive cardiomyopathy (CM) it was 9 1 mm ± 0 8 S D and a mean of 17 8 mm in four patients with IHSS (P < 0 01) In five patients with mitral stenosis the septal thickness did not differ from normal (mean 7 1 mm ± 0 9 S D) Septal motion was correlated with angiographic ejection fraction pattern of left ventricular wall motion and coronary angiography All patients with left ventricular disease and an abnormal septal motion invariably had significant left ventricular dysfunction at cardiac catheterization particularly patients with CM or severe CAHD although a normal septal motion does not exclude severe left ventricular dysfunction and hypokinesis

It is concluded that study of the interventricular septum by echocardiography provides a noninvasive technique with a high specificity but a lower sensitivity for identifying patients with left ventricular dysfunction

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Coronary artery disease in young patients Arteriographic and clinical review of 40 cases aged 35 and under

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Prior to World War II coronary artery disease (CAD) was considered to be uncommon in patients under 40 years of age Interest in the subject was stimulated by Yater and co workers[1,2] whose extensive clinical and pathologic reviews involving 866 cases from the files of the Armed Forces Institute of Pathology and the Veterans Administration were published in the immediate postwar years The problem was brought into sharper focus when Enos Beyer and Holmes[3] published their pathologic studies on CAD in young soldiers killed in the Korean conflict Since then other papers have appeared in the American literature each one serving to emphasize that the manifestations of CAD may become apparent in the younger age groups[4,5] CAD in young people is now recognized as a major problem in the Soviet Union according to the recent review of the Russian literature by Simonson and Berman[6]

Previously published morphologic studies of CAD in younger age groups have been made on autopsy material[1,2,7] Welch and co workers[8] were the first to publish results of coronary arteriographic studies in patients less than 40 years of age Their study dealt primarily with distribution of lesions and correlation with levels of serum cholesterol and did not include data on other clinical parameters It is the purpose of this paper to report on our experience with 40 patients aged 35 or less with CAD proved by coronary arteriography and correlated with a variety of clinical information These patients are compared to 20 other patients aged 35 or less who were studied for similar reasons and who did not have identifiable CAD by coronary arteriography

Methods

Sixty patients aged 35 or less who underwent coronary arteriography for suspected ischemic heart disease form the basis of this report The indications that were primarily responsible for this study were as follows (1) Twenty two patients presented with a history of chest pain that was regarded as (a) typical angina pectoris based on location and quality of the pain as well as its precipitation by exertion and relief by rest or nitroglycerine or (b) atypical angina pectoris i e chest pain that had atypical characteristics but was not definitely distinguishable from angina pectoris (2) Twelve patients had a history of chest pain that was diagnosed as a myocardial infarction by the referring physician. Adequate documentation however was frequently not

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Table I Discriminating features in Groups 1 and 2

Discriminating feature	*No of patients in Group 1*	%	*No of patients in Group 2*	%	*p value*
Typical angina	11/20	55	26/40	65	>0 05
Atypical angina	6/20	30	4/40	10	>0 05
History of infarction	6/20	30	31/40	77	<0 05
Family history of CAD	7/20	35	14/40	35	>0 05
Smoking	14/18	78	38/40	95	>0 05
Hypertension	4/20	20	4/40	10	>0 05
Obesity	3/20	15	9/33	27	>0 05
Fourth heart sound	3/20	15	23/39	59	<0 05
Abnormal ECG	16/20	80	32/39	82	>0 05
Non specific ST T	11/20	55	12/39	31	>0 05
Infarct patterns	5/20	25	20/39	51	>0 05
Positive stress test	2/17	12	11/28	37	>0 05
Lipoprotein abnormality	8/16	50	24/35	68	>0 05
Diabetes mellitus	2/14	14	3/33	9	>0 05

available These patients did not complain of sub sequent chest pain (3) Twenty three patients had a history of both myocardial infarction and subsequent chest pain either typical or atypical for angina pectoris (4) Three patients had elec trocardiographic changes that were charac teristic of a previous myocardial infarction and no history of chest pain

Patients with valvular aortic stenosis, idiopathic hypertrophic subaortic stenosis, or the mid systolic click late systolic murmur syndrome were not included in this study

A history and physical examination were per formed on each patient by at least two car diologists Blood sugars, serum cholesterol and triglycerides, and serum lipoprotein elec trophoresis[9,10] were performed according to stan dard techniques Submaximal exercise tests were performed on the treadmill Exercise was per formed at a 10 per cent grade starting at 1 m p h with subsequent increases in speed until angina or extreme exhaustion occurred or until the sub maximal predicted heart rate was achieved A positive test was defined as at least 1 mm of flat or downsloping ST segment depression in one or more leads for at least 0 08 seconds. Coronary ar teriography was performed according to the technique described by Judkins[11]

Based upon the results of coronary arteriogra phy the patients were then placed into one of two groups Group 1 consisted of patients who demon strated normal coronary arteries They also had normal right and left heart catheterizations. Group 2 consisted of patients with one or more obstructive lesions in the coronary arteries It must be emphasized that patients who were placed into Group 1 on the basis of the results of coronary arteriography were originally selected for catheterization for the same reasons as the Group 2 patients and obviously cannot be con sidered representative of randomly selected nor mal patients of this age group Hence, they can not be considered as normal control subjects, but serve only as a group of patients who have simi lar clinical features to Group 2 but differ in that their coronary arteries are normal

The severity of the lesions was classified on the basis of the following quantitative criteria a score of 1 indicated a lesion of less than 50 per cent of the diameter of the vessel was present 2 indicated a 50 to 75 per cent obstruction, 3 indi cated a 75 to 90 per cent obstruction, 4 indicated a greater than 90 per cent obstruction and 5 in dicated complete obstruction of a vessel

Certain features of the clinical picture that might be expected to have discriminatory value in separating Groups 1 and 2 were analyzed. These were as follows history of typical chest pain, history of atypical chest pain, *history* of myocardial infarction, *family history* of CAD in the immediate relatives cigarette smoking, history of hypertension, presence of a fourth heart sound, abnormal lipoprotein elec *trophoretic pattern*, elevated blood sugars, ab normal resting electrocardiogram, and positive *treadmill test* These 12 possible discriminating

features of Groups 1 and 2 were compared, utilizing the chi square test, in order to determine which of these features would have been useful in separating patients with normal coronary arteries from those with abnormal coronary arteries without resorting to coronary arteriography

Results

Sex and age distribution Group 1 (normal coronary arteries) consisted of 16 males and 4 females The mean age was 31 0 years with a range of 20 to 35 years Group 2 (abnormal coronary arteries) consisted of 35 males and 5 females The mean age was 32 0 years with a range of 22 to 35 years.

History and physical examination The results are summarized in Table I The incidence of the following features was not significantly different in the two groups typical angina atypical angina, positive family history cigarette smoking hypertension and obesity A history of a myocardial infarction and the presence of a fourth heart sound were significantly more frequent ($p < 0.05$) in Group 2 Only one patient in Group 2 was in congestive heart failure He had experienced two well documented myocardial infarctions A third heart sound was present in two other patients in Group 2 but there was no other evidence of heart failure No patient in Group 1 had a third heart sound. One patient in Group 2 had an abnormal systolic bulge in the midclavicular line Otherwise examination of the apex was normal in the remainder of the patients

Electrocardiogram In Group 1 the resting electrocardiogram was abnormal in 16 out of 20 patients (80 per cent) In 11 patients, nonspecific ST T changes were present and five patients had Q waves of 0 04 second duration that were consistent with previous myocardial infarction In Group 2 the resting electrocardiogram was abnormal in 31 out of 39 patients (80 per cent) In 12 patients nonspecific ST T changes were present and in 17 patients there were wide Q waves that were consistent with previous myocardial infarction The frequency of both nonspecific ST T changes and wide Q waves was not significantly different ($p > 0.05$) in both groups

Twelve patients in Group 1 had a treadmill test and in two patients (12 per cent) the test was positive Ten out of 30 patients (33 per cent) in Group 2 had positive electrocardiograms The incidence of positive treadmill tests in both groups was not significantly different ($p > 0.05$)

Metabolic studies Lipoprotein electrophoretic patterns were obtained in 16 Group 1 patients and were abnormal in eight (50 per cent) Type IV patterns were present in six patients and Type II patterns were present in two patients. Abnormal electrophoretic patterns were present in 24 out of 35 Group 2 patients (68 per cent) Type IV patterns were present in 16 patients and Type II patterns were present in 8 patients.

Blood glucose studies were available in 14 pa

Table II Distribution of major lesions (>50 per cent)

Arterial involvement*	No of patients	Per cent of total
1 Main left only	0	0
+ AD	0	0
+ Circ.	0	0
+ Right	0	0
+ AD + circ	0	0
+ AD + right	0	0
+ Circ + right	0	0
+ AD + circ. + right	1	2.5
2 AD only	10	25 0
+ Circ	2	5 0
+ Right	3	7 5
+ Circ + right	8	20 0
3 Circ only	5	12.5
+ Right	2	5.0
4 Right only	9	22.5
Total	40	100 0

AD = anterior descending Circ. = circumflex.

Table III Number of affected arteries* per patient

	Number	% of total
One artery	24	60 0
Two arteries	8	20 0
Three arteries	7	17 5
Four arteries	1	2.5
Total patients	40	
Total arteries	65	
Number of arteries per patient	1 6	

*Arteries with lesions narrowing the lumen diameter by 50 per cent or more

Table IV Summary of Group 1 patients

Pt.	Age/ sex	Angina typical	Angina atypical	History of AMI	FH/ CAD	Smoking	HBP	Obese	S_4	ECG-ST T	ECG MI	Positive treadmill	HLP	Abn. glu.	Coronary score
Normal coronary arteries															
1	35/F	+	–	–	–	NA	+	+	–	+	–	+	N	NA	–
2	30/M	+	–	–	–	+	–	+	–	+	–	–	IV	NA	–
3	34/M	+	–	–	+	+	+	–	–	–	–	–	IV	–	–
4	33/M	+	–	–	–	+	–	–	–	–	–	–	NA	–	–
5	33/M	+	–	+	+	+	–	–	+	+	–	–	IV	–	–
6	31/M	–	–	–	+	+	–	–	–	–	+	–	NA	–	–
7	32/M	+	–	+	–	+	–	–	–	+	–	–	N	NA	–
8	32/M	+	–	+	–	+	–	–	–	–	–	–	NA	–	–
9	35/F	+	–	–	–	NA	–	–	–	–	–	+	N	–	–
10	30/F	–	+	–	+	+	–	–	–	+	–	–	N	–	–
11	34/M	+	–	+	–	+	–	–	–	+	–	NA	NA	–	–
12	33/M	–	–	–	–	+	–	–	–	–	+	–	IV	–	–
13	30/M	+	–	–	+	+	+	–	+	+	–	–	IV	NA	–
14	32/M	–	+	–	–	–	–	–	–	+	–	–	N	NA	–
15	30/M	+	–	+	–	–	–	–	–	–	+	–	II	+	–
16	29/M	–	+	–	+	+	+	+	–	+	–	–	II	+	–
17	20/M	–	+	–	–	–	–	–	–	+	–	NA	N	–	–
18	27/F	–	+	–	–	–	–	–	–	–	+	–	N	NA	–
19	35/M	–	–	+	+	+	–	–	+	+	–	NA	IV	–	–
20	29/M	–	+	–	–	+	–	–	–	–	+	–	N	–	–
Abnormal coronary arteries															
1	32/M	+	–	–	+	+	–	+	–	+	–	–	IV	–	8
2	35/M	+	–	–	–	+	–	+	–	+	–	+	IV	+	4
3	35/M	+	–	–	–	+	–	–	–	–	–	+	N	–	7
4	29/M	–	–	+	–	+	–	–	–	–	+	–	N	–	2
5	35/M	+	–	+	+	+	+	–	+	–	+	+	II	NA	10
6	30/M	+	–	–	–	+	–	–	–	+	–	+	N	–	4
7	35/M	+	–	+	+	+	–	–	+	–	+	+	IV	–	18
8	29/M	+	–	+	+	+	–	–	–	–	+	–	II	+	5
9	32/M	+	–	+	–	+	–	–	–	–	+	–	II	–	13
10	34/M	+	–	+	+	+	–	–	+	+	–	+	IV	–	4
11	35/M	+	–	+	–	+	–	–	+	–	+	–	N	–	5
12	32/F	+	–	+	+	+	–	+	–	–	+	–	II	–	10
13	35/F	+	–	+	+	+	–	–	+	–	+	+	IV	–	23
14	34/M	+	–	–	+	+	–	–	+	–	–	–	IV	–	6
15	23/M	+	–	+	+	+	–	+	+	+	–	+	II	–	9
16	29/M	+	–	+	–	+	–	–	+	–	+	–	IV	–	5
17	31/F	+	–	+	+	+	–	–	+	–	+	N	II	NA	17
18	35/M	–	–	–	–	–	+	+	–	–	+	–	IV	–	10
19	32/M	–	–	+	–	+	–	–	+	–	+	–	N	–	5
20	35/M	+	–	–	–	+	–	–	+	–	–	–	N	–	5

Abbreviations M = male F = female AMI = acute myocardial infarction, FH/CAD = family history of coronary artery disease HBP = history of hypertension S4 = fourth heart sound ECG ST T = nonspecific ST T changes on electrocardiogram ECG MI = infarction patterns on electrocardiogram, HLP = hyperlipoproteinemia, II = Type II HLP IV = Type IV HLP N = normal Abn. Glu. = blood glucose abnormality NA = not available, + = present – = absent.

tients in Group 1 and two patients had an abnormal oral glucose tolerance test (14 per cent) Blood glucose studies were available in 33 patients in Group 2 Two patients had an abnormal oral glucose tolerance test and one patient, a known diabetic, had a fasting blood sugar of 150 mg per cent Thus 9 per cent of the patients in Group 2 were considered to have diabetes mellitus

Results of coronary arteriography in Group 2 (Table II) The anatomic distribution of significant obstructive lesions i e, 50 per cent or

Table IV Summary of Group 1 patients—Cont d

Pt.	Age/ sex	Angina typical	Angina atypical	History of AMI	FHI CAD	Smoking	HBP	Obese	S_4	ECG-ST T	ECG MI	Positive treadmill	HLP	Abn. glu.	Coronary score
Abnormal coronary arteries.															
21	33/F	−	−	+	−	+	−	+	+	−	+	−	N	+	5
22	35/M	+	−	+	NA	+	−	NA	−	−	−	NA	NA	−	5
23	32/M	−	−	+	−	+	−	NA	+	−	−	NA	NA	NA	5
24	35/M	+	−	+	−	+	−	NA	+	+	−	NA	NA	NA	9
25	22/M	−	−	+	−	+	−	NA	NA	−	+	NA	N	NA	4
26	25/M	−	−	+	−	+	+	NA	−	+	−	NA	NA	N	2
27	35/M	−	−	+	−	+	−	NA	+	−	+	−	NA	N	12
28	33/F	−	+	−	+	+	−	NA	+	+	−	−	IV	NA	2
29	30/M	+	−	+	−	+	−	+	+	−	+	NA	N	N	7
30	33/M	+	−	+	+	+	+	−	+	−	+	+	IV	N	7
31	34/M	+	−	+	−	+	−	−	+	−	+	+	II	N	13
32	25/M	−	−	+	−	+	−	−	+	−	+	NA	N	N	2
33	34/M	+	−	+	+	+	−	−	−	−	−	NA	IV	N	11
34	27/M	+	−	+	−	+	−	−	−	−	+	NA	II	N	3
35	34/M	−	−	+	−	−	−	−	−	−	−	NA	IV	NA	5
36	34/M	+	−	+	+	+	−	−	−	NA	NA	NA	IV	N	12
37	35/M	−	+	+	−	+	−	−	+	+	−	−	IV	N	8
38	33/M	−	+	−	−	+	−	+	−	+	−	−	N	N	3
39	32/M	+	−	+	−	+	−	−	+	+	−	+	II	N	6
40	32/M	−	+	+	−	+	−	+	+	+	−	−	IV	N	4

greater narrowing of the diameter of the lumen, is outlined in Table I The left anterior descending artery was involved in 60 per cent of the patients The right coronary and left circumflex arteries were involved in 57 5 per cent and 45 per cent respectively Involvement of the main left coronary artery was present in only one patient. The number of arteries involved per patient was 1 6

Single vessel disease was present in 60 per cent of these patients (Table III) When single vessel disease was present the right coronary and left anterior descending arteries were almost equally involved, with the left circumflex artery much less commonly involved.

Complete obstruction of one coronary artery was present in 22 patients and of two coronary arteries in three patients A total of 28 arteries were completely obstructed. Fifteen right coronary arteries 10 left anterior descending arteries, and three left circumflex arteries were completely obstructed.

The amount of obstructive disease based on the total coronary scores in Group 2 patients with and without a lipoprotein abnormality was compared, utilizing a one way analysis of variance by ranks[12] The 11 patients in Group 2 without a lipoprotein abnormality had a significantly smaller total amount of obstructive disease than the 24 patients in Group 2 who had a lipoprotein abnormality ($p < 0.05$)

A summary of the clinical information and coronary score of each patient is contained in Table IV

Discussion

Several authors have described lesion distribution in large series of patients studied with coronary arteriography [8,13,16] but there have been no reports dealing strictly with patients aged 35 or less Welch and co workers[8] studied patients less than age 40 at the Cleveland Clinic and although only one quarter of their patients were less than age 35 theirs is the one large series with an age composition that is closest to ours

The most commonly affected vessel in our study was the left anterior descending artery followed by the right and left circumflex arteries (Table II) This parallels the findings of the Cleveland Clinic Group both in the young patients[8] and in their larger series of unselected ages [13] Another similarity between our findings and the results of both of their series[8,13] is that the right coronary artery was most commonly obstructed. A major difference however is that we found single vessel disease in 60 per cent of our pa

tients, whereas Welch and co workers[8] found single vessel disease in only 36 per cent of their patients under age 40 A second difference of considerable significance is that we found 1 6 diseased vessels per patient whereas they found 2 3 diseased vessels per patient.[8] They also noted that the younger the patient, the less likely was a significant lesion to be present Consequently, our findings of fewer diseased arteries per patient and a greater frequency of single vessel disease is probably a reflection of a younger age group in whom it would be expected that the disease would be less far advanced

Among the several risk factors that have been associated with the development of CAD, lipid abnormalities have received widespread attention The presence of a hyperlipoproteinemia, especially Types II III, and IV of the Frederickson classification, is felt to play an etiologic role [16] In two series of patients with arteriographically proved CAD and unselected according to age the incidence of hyperlipoproteinemia was found to be 54 per cent[17] and 63 per cent.[18] A higher incidence of lipid abnormality was found to exist in the younger patients of Heinle s series who found that 80 per cent of 51 patients with an age range of 20 to 49 years had either Types II or IV hyperlipoproteinemia [17] However, 40 of these patients were age 40 or more Gofman Young, and Tandy[19] found that a hyperlipoproteinemia in younger patients (aged 30 to 39 years) was more reliable as a predictive index of myocardial infarction than in older age groups Our finding of a 68 per cent incidence of hyperlipoproteinemia in an extremely young age group (average age 32 0 years) with CAD indicates that hyperlipoproteinemia is no more frequent in young patients with CAD than in older age groups with CAD This is consistent with the 64 per cent incidence of lipid abnormality in 25 patients with premature CAD (average age 39 years) reported by Tzagournis, Seidensticker, and Hamwi [20] Furthermore, the fact that the incidence of hyperlipoproteinemia in Groups 1 and 2 of our study was not significantly different rendered a lipid abnormality of little value as a predictive index of CAD in the younger age groups

The clinical diagnosis of CAD is frequently a very difficult problem This is especially true in young patients who present with chest pain and also when a routine electrocardiogram reveals a pattern that is consistent with a previous myocardial infarction in a patient without a history of chest pain Certain features of the total clinical evaluation, short of coronary arteriography, may provide a rational basis upon which the diagnosis of CAD may be made or excluded. Characteristics of the chest pain, the presence or absence of risk factors, ' the physical examination, electrocardiogram, and exercise tests may be of value in discerning patients with CAD from those with normal coronary arteries.

We have analyzed 12 possible discriminating features (Table I) and have found that 10 of these were not useful in separating normal subjects (Group 1) from abnormal subjects (Group 2) While a history of chest pain that is typical for angina pectoris is frequently present in patients with CAD it has been found by others[21, 22] as well as by us that many of these patients have normal coronary arteriograms. On the other hand, while patients with atypical chest pain frequently do not have CAD it is well recognized that patients with CAD may have pain that does not conform to the classical description of angina pectoris.[23] Thus, the presence of either typical or atypical chest pain was not useful in separating Groups 1 and 2

Likewise, the incidence of a positive family history, cigarette smoking, hypertension, obesity, or the presence of hyperlipoproteinemia or diabetes mellitus provided no basis upon which the two groups could be distinguished Resting electrocardiographic abnormalities including ST T changes and infarct patterns, and abnormal treadmill tests offered little discriminating value Positive exercise tests have been found by others in patients with normal coronary arteriograms [24]

The incidence of only two of the 12 possible discriminating features, a fourth heart sound and a history of myocardial infarction were found to be significantly different in the two groups Whereas a fourth heart sound in a patient over age 40 has little diagnostic value, its presence in a younger patient is abnormal [25] We believe that its presence in a significantly greater percentage of patients with CAD than in normal subjects may provide a useful clue in separating these two groups However, in view of the occasional auscultatory confusion between a fourth heart sound followed by a first heart sound versus a split first heart sound phonocardiographic confirmation may be necessary

A history of myocardial infarction is reliable

only insofar as it can be clearly documented by the supporting evidence of a diagnostic electrocardiogram and enzyme changes As was true in our series this documentation is frequently not available when the patient presents to the physician Even if unequivocal evidence of a previous myocardial infarction is available, the possibility exists that the patient has normal coronary arteries Indeed, it is in the younger age group that this situation is most likely to exist. The literature contains at least 16 cases of well documented myocardial infarction in whom arteriography revealed completely normal coronary arteries and in whom the age was given [6 34] The average age was 30 2 years with a range of 16 to 43 years Fourteen of the 16 patients were less than 40 years of age Therefore it may be said that although a documented history of a myocardial infarction is a reasonably reliable indicator of abnormal coronary arteries in young patients it is not completely dependable in separating abnormal subjects from normal subjects Only coronary arteriography will allow this differentiation to be made with certainty

Gertler and co workers[35] have found that the long term prognosis for CAD is inversely related to the age at the first clinical episode In view of the profound implications regarding life expectancy in a young patient whose important family responsibilities and career planning are at stake we believe that coronary arteriography is a justifiable procedure in a young patient with a history of myocardial infarction or chest pain that is consistent with either typical or atypical angina pectoris in order to define the status of the coronary circulation

Summary

Coronary arteriography was performed in 60 patients aged 35 or less with suggested coronary artery disease (CAD) Twenty patients (Group 1) had normal coronary arteries and 40 patients (Group 2) had one or more obstructive lesions The left anterior descending artery was commonly involved followed by the right coronary and left circumflex arteries The right coronary artery was most commonly completely obstructed. Single vessel disease (50 per cent or greater obstruction) was found in 60 per cent of the patients, an incidence that is considerably higher than in studies of older patients. A total of 1 6 diseased vessels per patient was present A hyperlipoproteinemia (HLP) was found in 68 per cent of Group 2 patients Patients in Group 2 with an HLP had significantly more CAD than Group 2 patients with normal lipoproteins The incidence of the following clinical features were not significantly different in Groups 1 and 2 typical angina, atypical angina positive family history smoking hypertension obesity abnormal electrocardiogram positive treadmill test, HLP and diabetes mellitus A fourth heart sound and a history of a myocardial infarction were significantly common in Group 2 Since almost all of the previously reported cases of myocardial infarction with normal coronary arteries have occurred in young patients, history of a myocardial infarction does not assure the presence of obstructive coronary artery lesions. It is suggested that coronary arteriography is a justifiable procedure in a young patient who presents with a clinical picture that is either compatible with or cannot be clearly distinguished from CAD

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Incidence and treatment of the patent ductus arteriosus in the ill premature neonate*

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Several reports suggest an increased incidence of the persistent patent ductus arteriosus (PDA)† in the premature neonate[1-8] The reason is uncertain Newer methods of intensively treating prematurity and neonatal diseases may cause the ductus to remain open or to reopen after functional closure and result in more survivors with a PDA Pulmonary arterial structure in the premature infant[9,10] hypoxia[11,12] and other etiologies[3] to explain persistent patency have been proposed. The premature infant with a PDA often has respiratory insufficiency and congestive heart failure simultaneously[2-8] Some of the patients with refractory cardiorespiratory failure may require and benefit from surgical PDA ligation regardless of their poor clinical status[4,5,7,8,13]

This report summarizes a four year (July 1 1968 through June 30 1972) experience with 90 cases of PDA in the ill premature neonate The incidence diagnostic criteria and treatment methods are presented against which others can compare their experience An attempt is made to delineate in which type of patient, and when in the course of the disease surgery should be considered.

Methods and patient material

The data presented here were obtained from a retrospective review of patients charts All patients were treated in the Regional Neonatal Intensive Care Center at Madison, Wisc and came from a 14 to 16 county area with about 15 000 deliveries per year Approximately 40 per cent of the patients were delivered at St Marys Hospital Medical Center where the Unit is located and 60 per cent were transferred to the Center in an ambulance equipped with an Ohio Transfer Incubator (Ohio Medical Products Madison Wisc) A physician accompanied each transfer No attempt was made to separate the transfer and inborn population in the data tabulation

All patients suspected of having a PDA were seen independently by two of us (R D Z and M K L) and daily during their hospitalization (R D Z. and S N G) The roentgenograms were read by both a radiologist and a pediatric cardiologist. ECG reading and cardiac index measurements were made by one individual (M K L.) Infants who had evidence of a cardiac lesion in addition to a PDA were subjected to cardiac catheterization and were excluded from the study Patients with a murmur but without any associated signs of heart disease to establish a diagnosis of PDA, were also excluded.

The diagnosis of heart disease due to a PDA established on clinical criteria was made in 90 of 1 029 patients admitted to the Unit in the four

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†Abbreviations used n this manuscript are: PDA, patent ductus arteriosus, RDS, esp tory distress syndrome SGA, mall f gestat nal age, CNS entr l nerv us y tem, and ECG lectrocardiogram.

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Table III Patient care patterns

	1968 1969		1970 1971	
Total admissions	235		260	
Patients on respirator	13		36	
Patients with PDA on respirator	1		14	
Patients receiving albumin fresh frozen plasma, or fresh whole blood				
No evidence of PDA	14/44†		18/28†	
PDA with failure	5/6		15/19	
Intravenous fluids (c.c./Kg/24 hrs.) Day of life	*No PDA*	*PDA with failure*‡	*No PDA*	*PDA with failure*‡
1	83 ± 25	86 ± 26	96 ± 9§	110 ± 34§
2	114 ± 37	88 ± 13‖	119 ± 31¶	132 ± 34¶ ‖
3	137 ± 37¶	122 ± 31¶ ‖	145 ± 34	154 ± 30‖
4	137 ± 36	113 ± 36‖	161 ± 49	166 ± 43‖
5	153 ± 40	130 ± 37	155 ± 42	165 ± 47

Albumin 1 Gm. per kilogram or 10 c.c. fresh frozen plasma/blood per kilogram at least once during first five days of admission.
†Data taken from neonatal intensive care patients of same time period and with same weight distribution (< 000 grams) but without diagnosis of PDA 44 and 8 patients, respectively
‡Data available on only 6 to 12 patients in these groups.
§ $p < 0.01$
¶ $p < 0.001$
‖ $p < 0.05$

had severe respiratory distress syndrome but over half of the failure groups (B and C) had severe respiratory distress and 44 per cent required respirator therapy In these patients an umbilical arterial catheter was placed in the thoracic aorta at the level of the diaphragm for blood gas sampling An attempt was made to maintain the arterial P_{O_2} between 50 to 70 mm Hg and the pH above 7 25 Assisted ventilation was initiated when any of the following three criteria were present $Pa_{O_2} < 50$ mm Hg in FI_{O_2} of 90 per cent $PCO_2 > 80$ mm Hg or inadequate respiratory drive Twenty five of the 27 ventilated failure patients (groups B and C) met the assisted ventilation criteria by the second day of life The diagnosis of a PDA and cardiac failure was present before assisted ventilation in only three of those 30 PDA patients

Some patterns of patient care changed during the four year period. Examples for the period 1968 1969 and 1970 1971 are shown in Table III More patients were placed on assisted ventilation in the 1970 1971 year period, and a larger number of patients with a subsequent PDA were ventilated in 1970 71 (14 out of 36) than in 1968 1969 (1 out of 13) Plasma expansion and maintenance of blood pressure by the use of fresh frozen plasma fresh whole blood and albumin was more routine in 1970 1971 than in 1968 1969 and was almost always found in patients with a PDA and failure in either time period (Table III) More fluids were given the first five days of life in the 1970 1971 period than earlier but this only reached statistical significance ($P < 0.05$) between the PDA groups on Days 2 3 and 4 Patients with a PDA and failure also received significantly ($P < 0.01$) more fluids than the no PDA group on Days 1 and 2 of 1970 1971 (Table III) but the reverse was true on Day 3 of 1968 1969

Results

A harsh systolic ejection murmur ending before the second sound, most often heard with maximum intensity at the second left intercostal space radiating down the left sternal border and often to the back was the initial clinical finding noted with the PDA Rarely was the murmur continuous when it first appeared. The precordium was infrequently hyperactive Three fourths of the patients with subsequent failure (groups B and C) had the onset of their murmur in the first seven days of life Most infants (83 per cent) in these failure groups did not require

Table I Incidence of PDA in a neonatal intensive care unit

	1968 69			1969 70			1970 71			1971 72		
Admissions*	235			253			260			281		
PDA	6			30			39			15		
Incidence	2 5%			11 8%			15%			5.3%		
PDA vs. birth weight	*Total*	*PDA*	*%*	*Total*	*PDA*	*%*	*Total*	*PDA*	*%*	*Total*	*PDA*	*%*
<1 000 Gm	21	2	9 5	39	2	5 1	17	8	47 0	26	4	15 0
1 000 1 499	21	1	4 8	43	15	35 0	29	12	41 0	24	6	25 0
1 500 1 999	39	2	5 1	43	6	11 0	34	14	41 0	52	4	7 8
>2 000	154	1	0 6	128	7	5 4	170	5	2 9	179	1	0 5

Data tabulated from July 1 to June 30

Table II Characteristics of the ill premature neonate with a patent ductus arteriosus

Characteristics	*No failure No surgery (A)*	*Failure No surgery (B)*	*Failure Surgery (C)*
Number of patients	28	35	27
Female/male	14/14	23/12	17/10
Gestational age (wks)			
≤29	5	10	10
30 33	14	18	16
≥34	9	7	1
Birth weight			
≤1 0	2	8	7
1 0 2 0	20	18	18
>2 0	6	9	2
Respiratory distress syndrome			
Severe respirator therapy	3	17	10
Severe no respirator	4	6	6
Mild/lung water	11	4	4
Aspiration/pneumonitis	4	4	2
Other diagnoses (SGA asphyxia neonatorum etc.)	6	4	5
Deaths	1	12	9

year period (Table 1) The yearly incidence varied from 2 5 to 15 per cent A higher incidence occurred in infants of less than 2,000 grams (Table I)

The characteristics of the 90 patients in this series are shown in Table II The female to male ratio was approximately 3 to 2 The gestational age of 80 per cent was ≤ 33 weeks, with the majority of the patients born at 30 to 33 weeks gestation Eighty one per cent (73) of the patients had a birth weight of less than 2 0 kilograms with 19 per cent (17) less than 1 0 kilogram One group of 28 patients (A) had evidence of a PDA, but no cardiac failure (Table II) A second group (B) of 35 patients went into cardiac failure and were treated with digitalization and diuretics The third group (C) of 27 patients had cardiac failure, were treated medically for 2 to 22 days failure, and then the ductus of each was ligated surgically Digitalization was attained using Digoxin intravenously at a dose of 0 04 to 0 06 mg per kilogram total digitalizing dose (1/3 to 1/4 that dose as daily maintenance) and diuresis with ethacrynic acid 1 mg per kilogram, intravenously

In patients without failure (A) only 25 per cent

Table IV Deaths in the ill premature neonate related to the PDA

No surgery

Gestation (weeks)	*Birth weight (Gms.)*	*Admission diagnosis*	*Treated for failure (day)*	*Age at death (day)*	*Postmortem findings*
26	850	Premature	7	20	PDA BPD visceral congestion
28	779	RDS	13	18	PDA, pulmonary hemorrhage diffuse vascular congestion
30	1 559	RDS	15	60	PDA, visceral congestion
32	2 150	RDS PROM	3	17	PDA, BPD visceral congestion
32	1 276	RDS TWIN	7	11	PDA, BPD pulmonary hemorrhage visceral congestion

After PDA surgery

Gestation	*Birth weight (Gms.)*	*Treated for failure (day)*	*Operative*		*Death (Days postop)*	*Complications*
			Age (day)	*Weight (Gms.)*		
26	907	21	43	900	1	BPD *E. coli* pneumonia
26	737	4	7	567	3	Postoperative hypoxia endotracheal tube displacement
26	907	9	22	980	55	BPD
27	1 000	7	8	950	3	Ligate pulmonary artery
29	950	10	26	1 120	10	Atelectasis, mucus plugs
30	1 417	10	16	1 247	45	BPD atelectasis
30	1 276	4	26	1 276	1	BPD endotracheal tube misplacement
30	1 134	11	13	1 150	1	Duct avulsed repaired. postoperative under ventilation
34	1 960	11	14	1 700	5	BPD cystic fibrosis

BPD bronchopulmonary dysplasia.
PROM Rupture of membranes > 24 hours

Twenty two of the 90 patients in this series died (Table II) Eight of the deaths were not directly related to congestive heart failure but occurred primarily due to prematurity hypoxia and CNS hemorrhage Fourteen deaths were attributed to the PDA (Table IV) Five patients with persistent signs of failure and no improvement were not taken to surgery but were given diuretics repeatedly They succumbed to cardiorespiratory failure At autopsy a large PDA and diffuse visceral congestion was found in each Bronchopulmonary dysplasia was present in three of the five cases

There were no deaths in the operating room Five of the nine deaths in the surgery group were in patients with a birth weight and/or operative weight of ≤ 1 000 grams (Table IV) The survival rate in those over 1 000 grams was 80 per cent and ≤ 1 000 grams it was 30 per cent Histologic evidence of bronchopulmonary dysplasia was present in 5 of the 9 postsurgical deaths Postoperative medical and nursing management complications were a contributing factor in four deaths and in one patient the pulmonary artery was ligated (Table IV)

Discussion

Other small series have suggested that the incidence of the persistent PDA in the premature infant has increased.[2,7] This series supports that observation Possible etiologies suggested have been a decreased response to oxygen due to immature enzyme systems[19] and constrictor response[20] differences in muscular coat[9,10] or media[21] and frequent low Po_2 values[7] Certain patterns of care changed during the four year period presented here The survival rate of patients with RDS increased from 56 per cent in 1968 1969 to 79 per cent in 1971 1972 The use of respirators and blood product replacement was more frequent in

digitalization until three or more days after the onset of their murmur A diastolic murmur, bounding pulses, hepatomegaly, and apnea and bradycardia were the most frequently associated findings in patients with cardiac failure Peripheral edema or pulmonary râles were less reliable indications of failure in these patients

Roentgenographic evidence of perihilar edema and/or increased pulmonary vascularity[15] was found in 80 per cent of the cases These roentgenographic findings were present in over one third of the patients before the heart murmur was heard or clinical signs of congestive failure developed The cardiac size (per cent of the transthoracic distance) varied from 0 43 to 0 65 This index decreased in 7 out of 17 failure patients after digitalization, but decreased in only 1 out of 15 patients with persistent failure and subsequent surgery Surgery was followed by a decrease in cardiac size in 7 of these remaining 14 patients before discharge from the hospital In only 2 out of 32 patients treated for failure did the cardiac index increase

In the 81 patients in whom the ECG data was retrievable all but 5 patients had abnormal tracings (ECG criteria of references 16 and 17) Right ventricular hypertrophy was most common (60 patients) combined ventricular hypertrophy next (37 patients), and only three patients showed isolated left ventricular hypertrophy Sixty patients had two or more ECG's during their hospitalization Only one out of 20 patients without failure underwent a change in the ECG from right to combined ventricular hypertrophy, and three patients changed in the opposite direction In contrast 17 out of 40 patients in the failure group initially had right ventricular hypertrophy which changed to combined and only two patients changed from combined to right The ischemic pattern of T wave and S T segment shift was a common finding in infants in failure

The clinical diagnostic impression of a PDA was confirmed by direct means in 44 out of the 90 patients surgery, 27, autopsy, 12, cardiac catheterization, 3 and aortogram 2

Twenty seven patients underwent surgical ligation of the PDA The weight range was 567 to 2,013 grams with 7 $\leq$ 1,000 grams Twenty two patients had a gestational age of $\leq$ 33 weeks The indication for surgical intervention was failure of the patient to respond to medical therapy or deterioration after once having responded. Our impression was, in each instance that the patient could not survive without surgical therapy This situation occurred in 13 cases after 2 to 4 days of digitalization and diuretics, in eight cases after 6 to 11 days, and in three others after 14 to 22 days In two other patients bradycardia was so severe that an intravenous epinephrine drip was necessary, and these patients were taken to surgery One patient had the PDA ligated incidental to a left upper lobectomy for congenital lobar emphysema

The time the patient spent in transit and in the operating room was usually less than 1½ hours Most patients received a continuous infusion of isoproterenol (5 to 10 μg per kilogram per hour) during and following the operation to obviate problems with bradycardia Patients occasionally received atropine to offset bradycardia due to vagal stimulation Nearly all patients were anesthetized with a combination of halothane and an N_2O O_2 mixture Rapid ventilation was often essential The ligation of the duct was completed and the wound closed in an average of 30 to 40 minutes. Efforts were made to maintain the temperature above 97° F with a thermal mattress and heat lamp, but four infants had a temperature of less than 97° F after surgery Assisted ventilation was continued while the infants were enroute from the operating room to the Neonatal Intensive Care Unit. Twenty out of the 27 patients were ventilated postoperatively with intermittent positive pressure for one hour to several days Fluids were restricted to 70 to 80 ml per kilogram the first 24 to 36 hours after surgery Postoperative complications were frequent. In six patients, a persistent or recurrent pneumothorax occurred. Six patients had recurrent atelectasis and excessive mucus led to ventilation difficulties in several patients the latter occurring more frequently in patients with bronchopulmonary dysplasia Bradycardia despite adequate ventilation occurred in three of the patients and was treated for 1 to 3 days with isoproterenol One patient bled significantly from the wound and chest tube due to over heparinization from a fresh blood transfusion This was corrected with protamine sulfate One patient suffered a cardiac arrest and fibrillation in the operating room and required cardiac massage One patient had a left hemidiaphragm paralysis and required plication two weeks after the PDA repair

genographic evidence of perihilar edema and/or increased pulmonary vascularity and an abnormal electrocardiogram

Twenty seven patients underwent surgical ligation of the PDA There were no deaths in the operating room The survival rate in those over 1 000 grams was 80 per cent. Of those patients that died due to the PDA nearly 60 per cent had bronchopulmonary dysplasia as an associated finding

The authors wish to thank the physicians of the Madison and the South Central Region of Wisconsin for their patient referrals and for allowing us to use their patients in this report We also wish to acknowledge the nursing staff of the Neonatal Intensive Care Unit for their help in abstracting *data from patients charts that were used in the manuscript*

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patients with subsequent PDA and failure Some of these factors may have altered or contributed to the changing incidence of PDA in our series Though speculative, possibly these factors should be studied in a prospective manner

The diagnosis of a PDA was correctly made on *clinical criteria* The characteristic murmur of *the patent ductus* in the premature infant has been described by others [1,2,22 4] It rarely is present at birth, is rapidly changeable in character, comes and goes, has variable intensity and is frequently accompanied by other signs and symptoms such as accentuated peripheral pulses and a chest x ray with a perihilar edema or increased vascularity pattern [15] In severe RDS, the presence or absence of the murmur is probably a function of a changing pulmonary systemic resistance ratio, rather than a changing degree of patency of the ductus The early and frequent pattern of right ventricular hypertrophy in this series is probably due to the pulmonary hypertension associated with RDS [25] With partial recovery, a decrease in pulmonary resistance, and an increase in pulmonary flow the work of the left ventricle may increase thus causing the added occurrence of left ventricular hypertrophy which occurred in nearly one half of the patients in failure Since cardiac catheterization entails a considerable risk [6] we generally proceed with medical and surgical treatment on the basis of clinical findings alone In every case that underwent surgery, was subjected to aortography or was examined at autopsy the expected patent ductus was present, and was usually a structure as large as the aorta There was an associated lesion (small ventricular septal defect) in only two of these 44 cases

Certain clinical and laboratory findings aid in separating those patients in cardiac failure or who are likely to go into failure from those without failure A diastolic murmur bounding peripheral pulses and hepatomegaly were frequent with failure A greater per cent (75 per cent) of the patients that progressed to failure (Groups B and C) had their murmur the first week of life than did those without failure (20 per cent) Apnea and bradycardia also occurred frequently These apneic episodes were not caused by hypoglycemia, hypocalcemia, hyperthermia, chronic hypoxia or infection, but other possible etiologies for apnea, such as exhaustion or increased Pco_2 secondary to pulmonary congestion, were not evaluated Signs routinely used in older patients for the diagnosis of congestive heart failure, such as peripheral edema, râles, and tachycardia were usually not present in this group of patients

Earlier reports indicated that such infants usually would not require surgical ligation of their patent ductus [2,3,27] Recently, however several [4,5,7,13] have suggested surgical closure of the persistent PDA in the premature infant The difficulty arises in deciding which patient is unresponsive to further medical management and is, therefore, a candidate for surgery The decision in this series was based on the clinical course of the patient after digitalization and diuretics Unresolving cardiomegaly or hepatomegaly, increased pulmonary vascular congestion, and rising oxygen requirements or an increased frequency of apnea and bradycardia episodes requiring assisted ventilation were used as indications to proceed with surgery More objective laboratory measurements of deteriorating cardiopulmonary function could not be accurately evaluated retrospectively

Others [4,7,13] feel that early surgical intervention may be essential to the survival of infants with severe RDS and heart failure due to a PDA and suggest that permanent lung damage may occur from pulmonary edema superimposed on severe RDS [7] In our series, surgical ligation of the PDA in the ill premature infant over 1,000 grams had a survival rate of 80 per cent. Bronchopulmonary dysplasia [28] was associated with nearly 60 per cent of the deaths due to a PDA These facts support the opinion that early surgical intervention may be warranted in the course of the premature infant with a PDA and RDS

Summary

Two to 15 per cent of the patients admitted to a Neonatal Intensive Care Unit developed signs of cardiac disease due to a PDA In a four year period, of 90 patients with a diagnosis of the PDA confirmation was made in 44 (surgery, 27, autopsy 12 and aortography 5) Eighty per cent were 33 weeks gestation or less

Two thirds of the patients went into congestive heart failure Over ½ of these had severe respiratory distress and 44 per cent required a respirator The diagnosis of a PDA and cardiac failure was made clinically by the presence of characteristic murmur frequently accompanied by a diastolic murmur, bounding pulses, hepatomegaly apnea and bradycardia, roent

Table I Comparison of flow indices and associated parameters between normal and amputee groups

Normal subjects			*Nontraumatic amputees*	*Traumatic amputees*
Limb	*Flow/100 ml tissue/min. (± S.D)*	*Limb*	*Flow/100 ml tissue/min. (± S.D)*	*Flow/100 ml tissue/min. (± S.D)*
Right arm	8 23 ± 2 70	Right arm	6 82 ± 2 84	6 94 ± 2 57
Right thigh	6 35 ± 1 91	Amputated thigh	2 66 ± 1 96	3 11 ± 1 70
Left thigh	6 24 ± 1 85	Nonamputated thigh	4 15 ± 2 35	5 80 ± 2 66
Parameters	**Normal Right thigh**		**Nontraumatic amputated thigh**	**Traumatic amputated thigh**
Δ Vol /beat (ml)	0 095 ± 0 027		0 035 ± 0 024	0 047 ± 0 018
Pulse rate/min.	68 ± 9 1		72 ± 14 5	66 ± 6 6
Segmental resistance (Ω)	23 7 ± 7 2		28 0 ± 16 0	33 0 ± 13 3
Segmental volume (ml)	2 298 0 ± 400		1 484 0 ± 704	1 152 0 ± 641
Volume resistivity (ohm cm)	238 68 ± 72 51		178.57 ± 143 74	137 09 ± 18 92
Parameters	**Normal Left thigh**		**Nontraumatic nonamputated thigh**	**Traumatic nonamputated thigh**
Δ Vol /beat (ml)	0 092 ± 0 023		0 058 ± 0 03	0 089 ± 0 040
Pulse rate/min	68 ± 7 8		70 ± 15 0	62 ± 8 7
Segmental resistance (Ω)	24.0 ± 7 1		25 5 ± 14 0	26 2 ± 15 6
Segmental volume (ml)	2 214 0 ± 459		1 861 0 ± 934	1 234 0 ± 353
Volume resistivity (ohm cm)	229 29 ± 64 47		202 26 ± 158 6	125 47 ± 34 40
Parameters				
Age (yrs)	28 3 ± 6 1		64 0 ± 11 16	42 3 ± 19.2
Systolic pressure (mm. Hg)	123 6 ± 11 3		158 2 ± 23 5*	122 5 ± 5 00
Diastolic pressure (mm Hg)	71 7 ± 8 6		83 0 ± 7 8	81 0 ± 2 0

*Indic tes p obability value of $p \leq 0.01$ f r the difference betw en the normal and mputee gr up ariable.

time Therefore the amplitude of the observed beat requires significant correction upward for this venous feedback if it is to be a valid index of flow As indicated in Fig 1 the ΔV and ΔR pulses are extrapolated backward along the early runoff slope through the earliest peaking to its intercept with the ordinate of initial rise time The flow index is based on the product of this corrected value equivalent to a stop flow stored pulse volume and the pulse rate The final flow index is expressed as volume per minute per 100 ml segment of thigh

Variations in pulse volumes are qualitatively and quantitatively judged from the height of the records when compared to its volumetric standard height (Fig 2) The subjects were studied in recumbency at ambient room temperature of 25 C The thighs were slightly raised on a pillow or at phlebostatic levels Medication smoking and other conditions were not controlled in the patients before the test but these activities were questioned in the control subjects. The pulse recording procedures take from 1 to 2 hours Each of the 2 amputee groups was compared to the normal group using the standard Student t test. Comparisons within groups were carried out via paired t tests In each case values of $p \leq 0.05$ were interpreted as evidence of a statistically significant difference

Results

There is no evidence that the electrical impedance flow indices of the right arms of the normal group are significantly different from those of either the nontraumatic or traumatic amputee groups (see Table I) Such flow indices for the amputated thighs of both the nontraumatic and traumatic groups are significantly lower than

Blood-flow indices in amputee and control limbs by mutual electrical impedance plethysmography

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James A Sedensky, Ph D
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A pilot statistical correlation of noninvasive indices of blood flow is derived from amputee and nonamputee thighs These are based on *mutual* electrical impedance measurements at 100 KHz and a 1 mA level The mutual electrical impedance plethysmograph was selected for solving this complex volumetric problem objectively This all electrical approach is favored because surface impedance electrodes can best physically define the dynamic and static segmental volemic conditions without imposing undesirable occlusion counterpressure, or crude air tight encasement which is always required for mechanical plethysmography The flow indices present in *22 amputee* thighs are compared with their nonamputated contralateral thighs and both thighs of *20 normal subjects* The reasons for amputation are nontraumatic diseases or a traumatic incident The differences in flow indices are indicative of marked alterations in circulatory status imposed by lower limb amputation

Method

We employed our own custom built impedance unit and a customized analogue computer to transform resistive impedance pulses (ΔR) into volumetric pulses (ΔV) Mutual electrical impedance implies a *four electrode* technique in which adequate electrode isolation is present. Under these conditions equivalent impedance values are obtained upon physically interchanging positions of the transmission and detector pairs When only *two electrodes* are involved in the study of ionic conductors such as the thigh the *self impedance* at small or large electrode interfaces greatly increases the numerical error of the base resistance observed and the volume calculation dependent on it

The tetrapolar (mutual) method is fully described elsewhere[1-6] and is sketched in a model in Fig 1 and as applied to the limbs in Fig 2 The device has a range of 0 to 1,000 ohms and recordability of 10 milliohms as indices for measure of displacements In addition, there is a first derivative pulsatile volume output (ΔV/sec) for coinciding velocity effects within the arteriovenous difference displacement pattern (Fig 2) In our experience these measures are satisfactory for studying any limb or torso segment plethysmographically with respect to its base pulsatile, and derivative impedances.

The pertinent equation for transforming resistances and linear dimensions to changes in volume flow (milliliters per minute) is

$$\Delta V/\text{min} = \rho\ (L^2/\bar{R}^2)\ \Delta R\ \text{Pulse rate} \quad (1)$$

Here, ρ is the volume resistivity of whole blood (assumed as 150 ohm cm), $\bar{R}$ is the average resistance in ohms of the segment L is its length in centimeters and ΔR is the effective or calculated change in ohmic resistance per given beat The volume pulse effects a change in *electrical conductance* defined as $\Delta R/\bar{R}^2$ related to cyclic dynamic storage and flow per beat The observed ratio $\bar{R}^2/\Delta R$ is the so called *parallel resistive shunt* produced by the blood entering and then leaving the given segment

There is venous runoff during systolic rise

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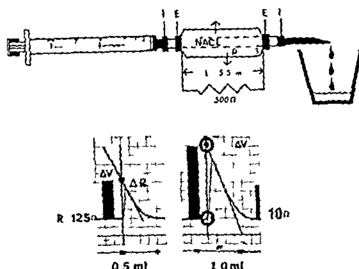


Fig 1 Tubular flow model pulses Extrapolation for stop-flow systolic volumes A flow test model based on tetrapolar (mutual) electrical impedance measures and Equation 1 An expansile tube or artery (======) is connected to electrode pairs IE EI and filled with electrolyte of known ρ The base resistance is read from the bridge or voltohmmeter (125 Ω) The change in resistance or volume is noted (black bar) with expansion to 0.5 ml. and 1 0 ml. against a closed stopcock However if a run off is provided during injection, the electrolyte will feed back to a collecting reservoir The volume of electrolyte (ΔV) stored in the tube at any time is revealed by the pulse curve The run off slope of the pulse will vary with the run off hindrance to flow Under these conditions, the detected volume of electrolyte will never reach the ideal peak value obtained in the case where there is in finite hindrance to outflow due to a completely closed stopcock The ideal value is obtained from the pulse by retrograde extrapolation of the run off slope to zero pulse time These values of the idealized volumes calculated from Equation 1 using the extrapolated impedance data are equivalent to 0 5 ml and 1 0 ml. per pulse These calculated volumes agree with those actually delivered from the syringe

than the corresponding values in the normal group (Table I) *Within* each of the 2 amputee groups however there are no statistically evi dent differences in volume resistivity between the amputated and possibly more normal nonam putated thighs (Table II)

As seen in Table I systolic blood pressure shows a significant elevation in the nontraumatic group (158 2 mm Hg) as compared to the normal and traumatic groups (123 6 and 122 5 mm Hg) This unfavorable difference in peak driving pressure indicates a probable higher peripheral arterial hindrance in the nontraumatic am putees This is also reflected physiologically in the slightly elevated diastolic pressures of the amputee groups compared to the normal group

Other objective data collected from the above groups indicate that the mean age of 64 years in the nontraumatic group is significantly higher than the mean age of 28 years in the normal group and 42 years in the traumatic group These age differences possibly influence the circulatory function measured. The medical history and find ings further reveal the following conditions in the *nontraumatic group* 9 cases of diabetes mellitus (existing between 1 to 20 years) 6 cases of different grades of obesity (4 of whom were also diabetic at the time of the study) 4 cases of anemia 5 cases of arteriosclerotic heart disease 5 cases of peripheral vascular disease 4 cases of hypertension 2 cases of unilateral sympathec tomy 1 case of bilateral sympathectomy 1 case of cerebral vascular accident, 1 case of syphilis (also had arteriosclerotic heart disease) and 1 case of Parkinsonism In the *traumatic group* the following conditions were observed. 1 case of diabetes mellitus 1 case of obesity 1 case of anemia 1 case of VDRL (weakly reactive) and 1 case of varicose veins. These numerous clinical deviations are consistent with modification of cir culatory functions in the amputee groups, partic ularly the nontraumatic group

Discussion

Blood flow is pulsatile and superimposed on a perfusion flow gradient. Flow detection by me

Table II Paired comparisons of flow indices and volume resistivity within groups

Flow/100 ml tissue/min.

Normal subjects			*Nontraumatic amputees*			*Traumatic amputees*		
Right arm	*Right thigh*	*Left thigh*	*Right arm*	*Amputated thigh*	*Nonamputated thigh*	*Right arm*	*Amputated thigh*	*Nonamputated thigh*
8.23 ml	6.35 ml	6.24 ml	6.82 ml	2.66 ml	4.15 ml	6.94 ml	3.11 ml	5.80 ml
*	NS	*	†	†		*, †	NS, †	*

Volume resistivity (ohm cm.)

Normal subjects		*Nontraumatic amputees*		*Traumatic amputees*	
Right thigh	*Left thigh*	*Amputated thigh*	*Nonamputated thigh*	*Amputated thigh*	*Nonamputated thigh*
238.68	229.29	178.56	202.26	137.09	125.47
NS		NS		NS	

N.S. Refers to probability value of $p > 0.05$ for the paired difference.
Refers to probability value of $p < 0.05$ for the paired difference.
† Refers to probability value of $p < 0.01$ for the paired difference.

those of the normal groups (6.35 ml. per minute per 100 ml. of tissue). The impedance flow index is lowest in the nontraumatic amputated limbs (2.66 ml. per minute per 100 ml. of tissue). Although the flow index in the traumatic amputated limbs (3.11 ml. per minute per 100 ml. of tissue) is significantly lower than in the normal group, there is no evidence that it differs from the nontraumatic amputee group.

Comparatively, the right arm flow indices are greater than those in the thighs in all 3 groups, except in the traumatic group where there was no difference between the right arm and the nonamputated thigh. These differences are tabulated in the paired comparisons shown in Table II.

As shown in Table I, the pulse rates of the amputee groups do not differ significantly from those of the normal group. The volume per beat per 100 ml. of tissue is significantly lower in the amputated thighs of both amputee groups compared with the nonamputated thighs of the normal group. On the other hand, these pulse volumes in the nonamputated thighs of the traumatic group are not statistically different from those in the thighs of the normal group. In the nontraumatic amputee group, however, the pulse volumes in the nonamputated thighs remain significantly lower than those in the normal group.

The physical nature of the thigh can be described by its segmental resistance, segmental volume, and the calculated volume resistivity. There are no characteristic differences in the segmental resistances among the 3 groups regardless of disease, normality, or amputation (Table I). With respect to the segmental volumes per 15 cm. of length of the amputated thighs, the values of both the traumatic and nontraumatic groups are significantly lower than those of the nonamputated thighs of the normal group. Only the segmental volumes of the nonamputated thighs of the traumatic group are significantly smaller than those of the normal group. With respect to volume resistivity, only the values for the amputated and nonamputated thighs of the *traumatic* amputee group are significantly lower

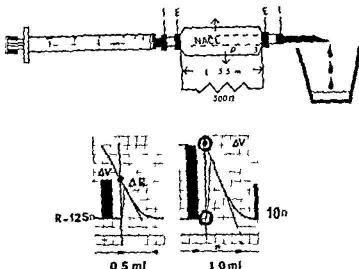


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Discussion

Blood flow is pulsatile and superimposed on a perfusion flow gradient. Flow detection by me

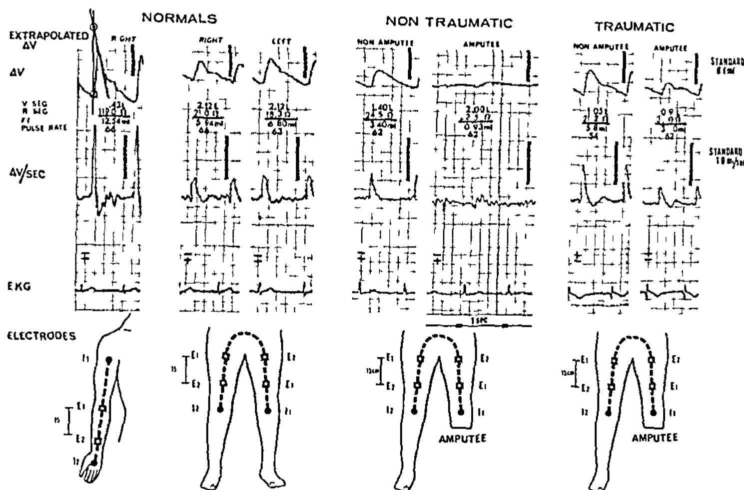


Fig 2 Representative computerized pulsatile impedance volumes (ΔV) per 100 ml. segment of the arm normal amputated and contralateral thigh shown with placement of small surface electrodes as indicated The patterned area between the small detector electrodes (E_1 E_2) is the pertinent region of observation of the segment as a resistive impedance to current between electrodes (I_1 I_2) The positive peak values shown in the derivative pulses (ΔV/sec) are used by some investigators as flow indices and in our study as relative flow indices of maximum systolic flow per 100 ml of segment Method of extrapolating volume or impedance pulses for derivation of stop flow data is shown in Fig 1 and illustrated here in the normal right arm pulsation *Case 1* is a member of the *normal* group with a blood pressure of 130/80 age 33, right thigh circumference 42 3 cm and left thigh circumference of 42 3 cm *Case 2* is a member of the *nontraumatic* group with a blood pressure of 190/100 age 72 amputated thigh circumference of 39 8 cm and nonamputated thigh circumference of 41 8 cm *Case 3* is a member of the *traumatic* group with a blood pressure of 120/84 age 31 amputated thigh circumference of 34 5 cm and nonamputated thigh circumference of 36 3 cm The values for volume of segment (V Seg) in liters (L) resistance of segment (R Seg) in ohms (Ω) flow indices (F I) per minute per 100 ml and pulse rates are given for each limb of 3 subjects and should be compared with the means in the table

chanical stop flow methods are not very feasible for the thigh regions under clinical situations However, the electrical characteristics of the thigh defining the arteriovenous volume pulse are satisfactory for the study of amputated and nonamputated segments as shown in Fig 2 The rate and volume of feedback is correctable by end systolic run off slopes in *in vitro* and *in vivo* observations of the pulsed volume according to Allison and Nyboer [7] The control of this feedback varies with static levels of the limb and other mechanical and neurophysiologic hindrances The derivation of a blood flow index from electrical data by mutual electrical impedance systems becomes meaningful and applicable to the present study of amputee as well as normal limbs These electrical approaches require no abnormal segmental compression nor air or water seals surrounding the segment, to obtain valid electrical volume pulsations for analysis of a given region

This volume pulse study of amputees indicates that the contralateral limbs of amputees have significantly better flow indices per *100 ml of* complex tissue than the amputated segments (Table II) The demand for resting blood flow is lowered in the amputee segments by *elimination* of the tissue beyond it Whether this difference of

flow is principally neurogenic or metabolic in origin cannot be answered in this study Adverse degenerative factors appear additive to lower the flow index in the nontraumatic amputee when compared to the traumatic amputee group (Table I) but there is no defensible statistically significant difference between the two groups On the other hand, compared to the normal group a circulatory debit is given the contralateral thigh of the nontraumatic group while none is apparent in the traumatic group This might indicate that traumatic amputees could fare as well in the below knee as in the above knee prosthetic adaptation whereas unpredictable circulatory complications may occur to interrupt below knee adaptation or rehabilitation in the nontraumatic group

Atrophy of disuse could account for some difference in segmental volume for a given length The normal subjects which are the youngest group have the largest thighs. The nonamputated thighs are fuller than the amputated thighs principally in the nontraumatic group These atrophic amputated limbs have a slightly higher but statistically nonsignificant, electrical resistance than the limbs of the normal group Unexpectedly the volume resistivity of the amputated and nonamputated thighs of the traumatic group are considerably lower than the normal group This greater ionic conduction could be ascribed to a nonapparent tissue edema. Future studies should include other measures such as height weight, surface area and skin fold thickness Other conditions of interest would be phantom limb syndromes, adaptability to prosthesis below or above knee amputations time of disability after amputation before the prosthesis becomes satisfactory and type of prosthesis If possible the impedance or flow indices should be obtained before and after the indicated amputations Medical indications for the procedures should be authenticated

Justification of a bioelectric method for flow based on intrinsic characteristics of blood shunting in tissue is mathematically sound. Poiseuille defined flow or volume/time equal to mean pressure/physical hindrance *It is not essential to know the pressure or hindrance to satisfy this equation if volume can be identified as well as time.* One should note that arteriovenous pulse volume is never the correct pulse volume since there is some outflow from the segment. The regional run off slope for each pulse may vary greatly with posture breathing and pulse rate therefore a series of 5 to 10 pulses is required to estimate the specific correction Thus in dealing with direct volume or analogic volume pulses, we must deal with this correction for run off Other schools[8,10] have dealt with the forward slope of systolic pulse volume and its correction or its maximum slope or its peak first derivative as an index of the peripheral flow or the cardiac stroke volume These approaches are also possible and technically easy but not necessarily valid for mechanical or electrical systems of pulse volume detection for regional or systemic flow implications We would add the impedance method to other noninvasive approaches to flow inclusive of occlusive[11] or nonocclusive venous inflow venous outflow or arterial occlusion by any volemic detection system. We feel the problems of regional blood flow of the thigh can be met in the clinic and at the bedside by intrinsic or extrinsic electrical impedance systems.

Summary

Arterial insufficiency is recognized in amputee segments of thighs by bioelectrical impedance indices of blood flow The radiofrequency method of volume detection is painless noninvasive and reproducible for diagnostic or therapeutic management of circulatory impairments It interprets complex changes in electrical conductances in real volumetric terms which are easily understood by physicians

Blood flow indices based on bioelectric impedance in the present study indicate a statistically significant circulatory deficit is present in the amputated thigh of traumatic and nontraumatic amputees Vascular and degenerative diseases are almost invariably present in the nontraumatic amputee group

We acknowledge grants in aid from the Michigan Sister Kenny Fund and the Michigan Heart Association as well as cooperative assistance in instrumentation technique and other tasks from Mrs. Patricia Panzer Miss Lynne Gallison, and Mr Charles Stilson from our laboratory Mr Kenneth Reid from Uniroyal Tire Company Dr Walter Gessert from Eastern Michigan University and Miss Dorothy Wagner from General Motors Corporation, Warren Mich.

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Evaluation of isoproterenol as a method of stress testing*

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Selective coronary arteriography has greatly enhanced the cardiologist s ability to arrive at an anatomic diagnosis of coronary artery disease There still exists however the need for a screen ing test applicable in the outpatient setting which can be applied safely and readily to a larger population Recently Wexler Juaita and Simonson[1] have described in a preliminary re port the use of isoproterenol as a method of stress testing The purpose of our study was to evaluate further the isoproterenol stress test in a group of patients undergoing diagnostic coronary arteriography and to compare its specificity and sensitivity to that of a standard treadmill exer cise test.

Methods

Thirty five patients who were scheduled for coronary arteriography and who met the follow ing criteria were studied (1) the resting 12 lead electrocardiogram (ECG) did not reveal evidence of S T segment depression (2) they did not clini cally or on ECG have evidence of ventricular hy pertrophy recent myocardial infarction or con duction abnormalities and (3) they had not taken any cardiac medications at least 48 hours before testing

All tests were done in the postabsorptive state The sequence of testing was determined by ran domization With 20 patients the isoproterenol test was done first and with 15 patients the tread mill exercise test was the first test performed The second test was performed after return to baseline of the patient s heart rate blood pressure and ECG or on the following day Coro nary arteriography was done within the next several days following stress testing

The isoproterenol test was performed as follows (1) a control ECG was done before and after infusion of 20 to 50 c c of 5 per cent glucose in water (2) isoproterenol in a concentration of 0 2 mg per 100 c c of dextrose and water was in fused at a rate of 1 to 2 μg per minute with con stant ECG monitoring of precordial Lead V_4 or V_5 until diagnostic S T segment depression devel oped, significant chest pain occurred, or a heart rate equal to at least 130 beats per minute was reached and (3) ECG Leads I II III aV_L aV_F, and V_4 through V_6 were monitored immediately after infusion and every two minutes for 8 to 10 minutes

The graded exercise test was (1) initiated with a warm up period of three minutes at a speed of one mile per hour and a 10 per cent grade (2) the speed was then increased by 0 5 miles per hour every three minutes, maintaining a grade of 10 per cent until a speed of four miles per hour was reached (3) the speed was then maintained at four miles per hour and the grade was increased by 2 5 per cent every three minutes (4) the test was terminated when exhaustion occurred such that the patient was unable to continue diag nostic S T segment depression developed or sig nificant chest pain occurred and (5) Leads V_4 or V_5 were monitored during exercise and Leads I II III aV_L aV_F and V_4 through V_6 were

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*The opi ns or ass rti ns ontain d here n re the pri ate views f the utho s nd a e n t to be construed as offi al s r flecting th vi ws of th Departme t f th Army or the D partm nt f Def nse

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Table I Results of treadmill exercise and isoproterenol tests

Tests	Normal patients (Total = 15)	Coronary artery disease patients (Total = 20)
Positive treadmill exercise test	1	10
Negative treadmill exercise test	14	10
Positive isoproterenol test	3	12
Negative isoproterenol test	12	8

monitored immediately after exercise and every two minutes for 8 to 10 minutes

The criteria used for either a positive treadmill or isoproterenol test was a flat or downward depression of the S T segment of at least 1 0 mm and lasting at least 0 08 second.

Coronary arteriography was performed by the standard Judkins technique with multiple views of each coronary artery and both cineangiographic and fixed film recording

A significant coronary lesion was defined as an obstruction seen on at least two views which resulted in 50 per cent or greater narrowing of the coronary arterial lumen

The treadmill and isoproterenol tests were read by the authors without prior knowledge of the results of the coronary arteriography

Results

Thirty five patients were studied by coronary arteriography and 15 patients were judged to have normal coronary arteries while 20 patients had significant coronary artery disease

The average age of the patients with coronary artery disease was 48 years There were 19 men and one woman The patients with normal coronary arteries had an average age of 43 2 years and 13 of the 15 patients were men The average heart rate with exercise testing was 152 beats per minute and with isoproterenol testing 141 beats per minute

The results of the treadmill exercise and isoproterenol tests are summarized in Table I

The isoproterenol test correctly predicted in 71 per cent of the patients whether or not arteriographic coronary artery disease would be found The treadmill tests resulted in correct predictions for 68 per cent of the patients There were ten (50 per cent) false negative results and one false positive result with the treadmill exercise test, while with the isoproterenol there were eight (40 per cent) false negative results and three (20 per cent) false positive results Ninety three per cent of patients with normal coronary arteriography had a normal treadmill exercise test, whereas only 80 per cent of patients with normal coronary arteriography had a normal isoproterenol test. The isoproterenol test correctly identified 60 per cent of the patients with positive coronary arteriography, whereas the treadmill test identified 50 per cent of the patients.

The incidence of chest pain occurring during treadmill and isoproterenol testing is summarized in Table II

Discussion

Exercise in the form of the Master s test and the graded exercise test has been widely applied as a means of assistance in the evaluation of ischemic heart disease[2,3] However, there are at times situations in which the exercise test cannot be readily used, for example, in the patient with limiting claudication chronic lung disease or other physical or psychological limitations which prohibit adequate exercise The sensitivity and specificity of the exercise test has also limited its use as an ideal screening test[4-7] In addition because of the required bodily movement during exercise a stable ECG tracing is sometimes difficult to obtain Atrial pacing has overcome this latter problem but has the disadvantage of requiring cardiac catheterization

The use of drugs as a means of stress testing was initially described by Levine Ernstene and Jacobson[8] who used subcutaneous epinephrine as a means of inducing angina in a group of patients with clinically diagnosed coronary artery disease and they compared this group s response to a small group of normal control subjects Although they felt the test was helpful, they recognized the dangers of the procedure and a subsequent negative report by Katz Hamburger and Lev[9] prevented its widespread use In more recent years various other drugs such as pitressin[10] ergonavine[11] and dopamine[12] have been de

Table II Incidence of chest pain occurring during treadmill and isoproterenol testing

Tests	Normal patients		Coronary artery disease patients	
	With chest pain	Without chest pain	With chest pain	Without chest pain
Positive treadmill	0	1	9	1
Negative treadmill	2	12	4	6
Total	2	13	13	7
Positive isoproterenol	0	3	8	4
Negative isoproterenol	6	6	5	3
Total	6	9	13	7

scribed as useful in the diagnosis of ischemic heart disease however none of these agents has gained widespread popularity

Isoproterenol is a beta stimulator which acts on the heart to increase myocardial contractility and heart rate and thereby myocardial oxygen consumption is increased.[13] The demand for oxygen during isoproterenol stimulation in a patient with coronary artery disease might be expected to be greater than could be supplied by the coronary circulation and ischemia could develop In this circumstance it has been demonstrated that lactate metabolism is depressed or reversed which indicates anaerobic metabolism[14,15] This property of isoproterenol to increase myocardial oxygen demand significantly has suggested its use as a means of stress testing In a preliminary report, Wexler Juaita and Simonson[1] described isoproterenol testing in a group of patients with clinical coronary artery disease and in an age matched clinically normal group They also administered isoproterenol to a younger clinically normal group They reported that the isoproterenol test was useful in separating the group with clinical coronary disease from the control groups and in addition noted that frequently ischemic changes occurred in the ECG before the onset of chest pain thus the test could be stopped before the occurrence of pain They reported no significant complications

We have found that the isoproterenol test could be administered easily and no significant complications occurred although one patient did have transient A V dissociation We have tested another patient (not included in this series) who had a short burst of ventricular tachycardia shortly after termination of the isoproterenol test but this converted spontaneously to normal sinus rhythm No other significant arrhythmias have occurred and isoproterenol testing appears to be safe although the experience with these two patients emphasizes to us that proper resuscitative equipment must be available when any form of stress testing is undertaken

In our study the isoproterenol test compared favorably to the exercise treadmill test when presence or absence of coronary artery disease was subsequently determined by arteriography The isoproterenol test correctly identified 71 per cent of the group and the treadmill test identified 68 per cent (both statistically significant at the 5 per cent level) The weakness found in both tests was the high incidence of false negatives i e patients with coronary artery disease by arteriography who had normal stress testing In this respect the isoproterenol test was slightly better, but neither test was dependable When combined, the results were slightly better with 14 of the 20 patients with coronary artery disease being correctly identified. The high incidence of false negatives requires further analysis. It may be that an adequate stress was not achieved, e g the average heart rate reached was only 138 beats per minute with the treadmill test and 131 beats per minute with the isoproterenol test. The treadmill test was stopped because of chest pain in five instances and because the patient felt he could not continue in five instances The isoproterenol test was terminated because of chest pain in six patients and because of heart rate reaching 160 beats per minute in two patients. When the heart rate of patients who had

positive treadmill or isoproterenol tests is compared to the group that did not, it is seen that the heart rate was slightly slower in the former group (136 beats per minute for the treadmill test and 120 9 beats per minute for the isoproterenol test) Probably a more important factor in the incidence of false negatives was the extent of coronary artery disease that was present in these patients Six patients who had a negative treadmill test had only one vessel involved and only three patients who had a positive test had single coronary vessel disease As previously reported in a paper from this institution[16] the incidence of false negatives in patients with single vessel disease was 65 per cent as compared to an overall false negative incidence of 38 per cent (using 1 0 mm S T depression as the criterion for a positive test) In our small group of patients the isoproterenol test was slightly better in identifying patients with single vessel disease, five such patients were identified.

It should also be appreciated that the criterion for coronary artery disease i e coronary arteriography is an anatomic test where the stress tests are dynamic tests and different information about the same disease process may be given by each For example the patient with a single coronary artery obstruction and a previous myocardial infarction may have eliminated the only area of ischemia and have a negative stress test, but he would show evidence of disease on coronary arteriography It remains however, that a negative treadmill exercise test cannot be taken as evidence that no coronary artery disease is present this also appears to be true with the isoproterenol stress test.

In contrast to the report of Wexler, Juaita, and Simonson[1] our patients frequently developed chest discomfort with the infusion of isoproterenol, usually this was before the onset of S T segment changes The reason for the difference is unclear We do recall from our earlier experience that two patients had prolonged pain apparently because the isoproterenol was infused too rapidly, however even with much slower infusion other patients have had pain Chest discomfort developed both in those with and those without coronary artery disease and the occurrence of chest discomfort was of no value in separating the two groups (Table II) Ushiyama and co workers[17] also noted a high incidence of chest pain with isoproterenol infusion

Summary

Thirty five patients undergoing diagnostic coronary arteriography were evaluated before catheterization by both a standard treadmill exercise test and by the intravenous infusion of isoproterenol in a concentration of 0 2 mg per 100 c c of 5 per cent dextrose/water at a rate of 1 to 2 μg per minute S T segment depression of 1 mm or greater of the ischemic type was considered to be a positive test. The isoproterenol test was comparable to the treadmill exercise test in predicting the presence or absence of coronary artery disease (71 per cent correct predictions with the isoproterenol test versus 68 per cent with the treadmill test) and was administered safely and easily The isoproterenol test had several advantages (1) the baseline is stable and the intraprocedure ECG can be more easily monitored, (2) the test can be applied in situations where exercise is impossible for example when a patient had severe claudication incapacitating pulmonary disease, etc (3) other monitoring such as phonocardiograms blood pressure etc can be easily obtained, and (4) cardiac catheterization is not required in contrast to stress by atrial pacing The isoproterenol test would appear to have a useful role in the clinical assessment of coronary artery disease

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Coronary artery occlusion and blood lipids

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Results of a number of epidemiologic studies have indicated that patients with elevated blood lipid levels show a higher incidence of cardiovascular disease than individuals with low or normal lipid levels [1-4] Investigations of patients with angiographically determined coronary heart disease have also demonstrated that most of these patients have high blood lipid levels. Falsetti and co workers[5] have studied a group of 27 patients with angiographically proved coronary disease and found 17 patients with abnormal lipoprotein pattern Heinle and co workers[6] have observed a similar proportion of abnormal lipoprotein distribution (54 per cent) in 126 patients with coronary luminal irregularity or stenosis Allard, Ruscito and Goulet[7] have reported on 129 patients who needed aortocoronary bypass surgery and found only 14 patients with normal blood lipid levels. In our initial study of 152 patients with aortocoronary bypass [8] all were found to have elevated plasma lipid levels

While an association between the incidence of coronary disease and abnormal blood lipid levels or lipoprotein patterns appears to be well documented little is known about the possible correlation between the extent or the sites of the coronary obstruction, age of the patients, and plasma lipid levels The availability of information on the angiographically ascertained coronary obstruction and plasma lipid levels in 481 patients undergoing diagnostic arteriography offered an opportunity to investigate this possible relationship The result of this study indicates that both advancing age and elevated plasma cholesterol levels may be of similar importance in the development of coronary obstruction

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Methods

A group of 481 male patients referred to St. Luke s and Wood Veterans Administration Hospitals, Milwaukee Wisc for a diagnostic angiographic examination were studied An inquiry of a larger group of such patients (620) by questionnaire indicated that about 67 per cent of them did not have any treatment for control of blood lipids, while about 28 per cent followed some dietary restrictions and 2 per cent of the patients received hypolipemic drugs The plasma lipid levels of the patients with dietary treatment—237 ± 45 mg per 100 ml for cholesterol and 151 ± 71 mg per 100 ml for triglyceride (mean ± standard deviation)—were similar to values of the patients without the treatment—230 ± 45 mg per 100 ml and 174 ± 168 mg per 100 ml, respectively The group receiving the drug treatment had higher levels for both plasma cholesterol (252 ± 43 mg per 100 ml) and triglyceride (218 ± 110 mg per 100 ml)

The coronary arteriography was carried out as described by Sones and Shirey[9] or Judkins[10] and the film reviewed by cardiologists experienced in the interpretation of the angiograms The degree of obstruction was rated as suggested by Rowe

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and co workers[11] however the scale was inverted, i e the score of the patient without any coronary obstruction was set as 0 and a patient with all three main coronary arteries totally obstructed was assigned a score of 300 Fasting blood samples were collected before angiography prior to heparin administration and analyzed for serum total cholesterol by an automated procedure[12] triglycerides[13] and lipoprotein distribution[14] Reproducibility of the triglyceride and cholesterol methods were determined by repeated assays of aliquots from a frozen pool of a standard serum at weekly intervals Results for this pooled serum were triglyceride 137 ± 3 6 mg per 100 ml. cholesterol 202 ± 4 9 mg per 100 ml. Coefficients of variation were 2 6 and 2 4 per cent, respectively Lipoprotein typing was carried out using the Friedewalt Levy and Fredrickson[15] and Fredrickson Levy and Lees[16] estimates of average age adjusted cholesterol content of the individual lipoprotein fractions in conjunction with the lipoprotein electropherogram Type III was confirmed by absence of the β lipoprotein band on disc electrophoresis[17]

Results

The pertinent data on the patients are compiled in Table I In comparison with values obtained with a general population[18,19] the abnormal lipid elevation in our patients was mainly confined to the plasma triglyceride fraction. This was also reflected in plasma lipoprotein distribution since only 34 or 7 2 per cent of the patients belonged to Type II while 193 or 41 2 per cent, belonged to Type IV No lipoprotein typing was done in 12 patients.

Because of some changes in the interpretation of lipoprotein types which occurred during the collection of data (i.e introduction of Types IIa and IIb) it was decided to use only the original plasma lipid values for the study of the various correlations. The possible association between the blood lipid levels and the degree of coronary blood flow obstruction as represented by the occlusion score was evaluated in several ways

1 Number of affected coronary arteries and blood lipids The association between the number of markedly affected coronary branches (75 per cent or more of the lumen blocked) and blood lipids is shown in Table II A consistent and statistically significant increase in mean plasma

Table I Information on average age plasma lipids, and other variables in the group of 481 patients

Age (years)	52 ± 7 6
Plasma cholesterol (mg./100 ml)	258 ± 55 7
Plasma triglyceride (mg /100 ml)	212 ± 133.2
Lipoprotein distribution (%)	
Type II	7 2
Type IV	41 2
Type III	0.9
Normal	50 7
Smokers (%)	62 0†
Hypertension (%)	35 0†

Mean ± standard deviation.
†Information obtained from medical histories of 248 patients.

cholesterol level occurred with an increase in the number of coronary arteries occluded. Patients with no markedly occluded arteries had lower triglycerides than those with occluded arteries however differences according to the number of arteries affected were small and not statistically significant.

The breakdown of the plasma lipid values according to the specific coronary arteries blocked for at least 75 per cent of their lumen is also shown in Table II The data indicate that no marked differences in plasma lipid levels were associated with occlusion of specific coronary arteries.

2 Coronary occlusion age and plasma cholesterol levels The data on the association of the extent of coronary impairment age and plasma cholesterol levels are shown in Table III The age ranges were selected to include the decade group around the average age

The lowest average coronary occlusion score 144 was observed in the group of patients less than 48 years of age with plasma cholesterol levels below the 225 mg per 100 ml. value However even at this relatively low plasma cholesterol level there was a statistically significant correlation between the progressing age and the increase in the coronary impairment (Groups A through G $P < 0.01$) In patients less than 48 years of age, the rise in plasma cholesterol levels was also connected with a statistically significant increase in the coronary occlusion score (Groups A through C $P < 0.01$) Similar but less marked, changes in the score were observed with

Table II Plasma cholesterol and triglyceride levels of patients having one, two, or three coronary arteries occluded to at least 75 per cent of the lumen

Coronary artery affected*	No. of patients	Plasma	
		Cholesterol (mg/100 mL)	Triglyceride (mg/100 mL)
None ≥ 75% occluded	46	222 ± 6 2†	177 ± 17 3
One	107	255 ± 5 0‡	218 ± 15 4
LAD	62	256 ± 6 7‡	214 ± 20 9
Right	36	256 ± 7 9‡	216 ± 20 7
Two	154	258 ± 4 1‡	208 ± 8 5
CIR + LAD	28	252 ± 8 0‡	195 ± 24 4
Right + LAD	68	262 ± 6 3‡	212 ± 12 2
Right + CIR	35	253 ± 9 8‡	222 ± 19 6
Three	174	269 ± 4 7‡	221 ± 10 6
Right + LAD + CIR	126	277 ± 5 4‡	233 ± 13 7‡

LAD = Left anterior descending artery
CIR = Circumflex artery
Because of the small number of patients having occlusion of the circumflex branch only or occlusion of lesser branches in combination with main branches, these data were not included in the table
†Mean ± standard error
‡P < 0 01 in comparison with the group without any major occlusion.

Table III The effect of age and plasma cholesterol levels on the coronary occlusion score

Age (years)	Plasma cholesterol (mg/100 mL)		
	< 225	225 274	> 275
< 48	144 ± 16 7 (26) (a)	178 ± 8 7 (54) (b)	202 ± 8 4 (52) (c)
48 57	172 ± 9 3 (74) (d)	188 ± 7 6 (89) (e)	213 ± 6 6 (75) (f)
> 58	205 ± 11 2 (35) (g)	199 ± 10 8 (46) (h)	198 ± 13 2 (30) (i)

Number of patients in parentheses
P < 0 05 a b a c a g b c d f d g
Mean ± standard error

progressing elevation of plasma cholesterol levels in patients 48 to 57 years of age (Groups D through F, P < 0 05), or with increasing age, in the group with a plasma cholesterol range of 225 to 274 mg per 100 ml (Groups B through F) In the groups of patients with plasma cholesterol over 275 mg per 100 ml or older than 58 years of age, the further effect of age or rise in plasma cholesterol levels on the occlusion score was minimal

3 Coronary occlusion age and plasma triglyceride levels A similar tabulation of the average coronary score was done for the three age groups and three ranges of plasma triglycerides (Table IV) The lowest score 165 was observed in patients less than 48 years of age having plasma triglyceride levels below the 150 mg per 100 ml mark, while the highest score 214, was seen in the group with plasma triglyceride levels over 220 mg per 100 ml and age over 58 years In contrast to the observation in the groups with the high cholesterol levels where the age effect was not apparent, the occlusion score in patients with high plasma triglyceride levels (over 220 mg per 100 ml) increased with age (Groups C through I P < 0 05)

Table IV The effect of age and plasma triglyceride levels on the coronary score

Age (years)	Plasma triglycerides (mg/100 mL)		
	< 150	150 219	> 220
< 48	165 ± 14 9 (34) (a)	188 ± 8 1 (46) (b)	185 ± 9 7 (52) (c)
48 57	173 ± 8 7 (88) (d)	192 ± 7 8 (71) (e)	209 ± 6 8 (79) (f)
> 58	186 ± 12 4 (43) (g)	206 ± 10 3 (35) (h)	214 ± 10 8 (33) (i)

Numbe f patients in parentheses
P < 0 05 c f c i d f
Mean ± standard erro

Table V The effect of age and plasma cholesterol and triglyceride levels on the coronary occlusion score

Plasma triglycerides (mg/100 mL)	Age Less than 52 years Plasma cholesterol (mg/100 mL)		Age 52 years and over Plasma cholesterol (mg/100 mL)	
	≤ 250	251+	≤ 250	251+
≤ 180	160 ± 9 2 (78) (a)	189 ± 11 7 (38) (b)	181 ± 9 4 (75) (e)	212 ± 8 1 (53) (f)
181+	184 ± 9 4 (51) (c)	196 ± 6 6 (79) (d)	208 ± 10 7 (40) (g)	206 ± 7 8 (67) (h)

Number f patients in parentheses
P < 0 05 a b, a d, f e g e h
Mean ± standard error

Similarly in patients over 58 years of age the increasing levels of plasma triglycerides appeared to be correlated with the coronary occlusion (Groups G through I)

4 Coronary occlusion age and plasma lipids combined Since the previous data indicated that the age lipid coronary score interaction for plasma cholesterol and triglycerides may differ a combined tabulation including all three factors was undertaken In order to maintain a sufficient number of patients in the individual groups, only two subgroups for each variable were employed for the age below or above the mean of 52 years for plasma cholesterol, below or above 250 mg per 100 mL and for plasma triglycerides, below or above 180 mg per 100 ml. The data as shown in Table V indicate that, at lower plasma cholesterol levels (< 250 mg per 100 ml) an increase in plasma triglyceride levels was associated with a rise in the occlusion score This occurred in both age groups. For instance in the younger patients (less than 52 years of age) the occlusion score in the low cholesterol and *low* triglyceride group was 160 ± 9 2 while in the low cholesterol *high* triglyceride group it increased by 24 points to 184 ± 9 0 In the older patients (over 52 years of age) the corresponding difference between the high and low triglyceride groups was 27 points (181 ± 9 4 and 208 ± 10 7) This occlusion enhancing effect of higher triglyceride levels was not apparent in patients with high cholesterol levels (over 250 mg per 100 ml) of either age group

Discussion

All patients in the present study had some somatic complaints suggesting involvement of the cardiovascular system and the group thus

does not represent a "normal" or "average" male population as encountered in some of the epidemiologic investigations[2, 3, 20] Furthermore, the group of patients consisted of individuals mostly in the 40 to 65 year bracket, many of whom would be expected to show atherosclerotic changes However the range of the occlusion score or of the number of markedly affected coronary arteries was large enough to allow some conclusions on the possible association between the risk factors and the extent of the coronary occlusion

The variables most clearly associated with occlusion of the coronary artery lumen were increase in plasma cholesterol levels and progression in age or changes in factors connected with progressing age The occlusion score of 200 or slightly over 200 which probably represents the highest score value compatible with survival, was reached by both older patients with relatively low plasma cholesterol levels and younger patients with high plasma cholesterol values (Table III) It would seem, therefore that even moderately elevated plasma cholesterol levels in older subjects may be associated with a similar risk of coronary artery damage as elevated plasma cholesterol levels in younger patients An increase in plasma triglyceride levels seemed to be less occlusive than a rise in plasma cholesterol levels however the presence of elevated plasma triglyceride levels tended to enhance the degree of coronary obstruction in patients with relatively low plasma cholesterol levels

The finding of marked coronary artery impairment at plasma cholesterol levels of 250 to 270 mg per 100 ml (Table II) again raises the question of "normal" or average plasma cholesterol values and their meaning A recent compilation of opinions from a number of investigators in the field of atherosclerosis[21] as well as the data from this study indicate the need for re evaluation of the accepted normal lipid ranges

The data in Table II indicate that the transition from the relatively patent coronary arteries to having one main branch occluded is associated with a larger change in plasma lipid levels than is the transition from one vessel involvement to the involvement of two or three vessels A similar difference in the progression of coronary lesions has been reported by Gensini and Kelly[22] They observed that the severity of the arterial lesion increases faster in patients who have developed some initial lesions already than in individuals without any visible coronary blood flow impairment. Bruschke Proudfit, and Sones[3] in a large series of patients, have also failed to see development of angiographically determined coronary occlusion when the initial observation was normal These findings suggest that either the patients consisted of several populations markedly differing in their plasma cholesterol levels and predilection for development of a significant arterial occlusion or that the development of atherosclerosis passes through a "threshold range" of plasma cholesterol levels after which the progress of occlusion accelerates at an increased pace

The data from Table II confirm the known predilection for the left anterior descending branch to be occluded However, this was not associated with any marked changes in the blood lipid levels when compared with the rarer single occlusion of the right coronary or with the combination of two coronary arteries affected. It would seem therefore, that some additional factors possibly anatomic in nature are operational in the determination of the occlusion sites

While not discussed in detail preliminary studies were also carried out to find out whether the calculated correlations between the age coronary occlusion score and plasma lipid levels were affected by an unequal distribution of other coronary risk factors, especially of hypertension and smoking Information obtained for about one half of the patients in each of the eight cells in Table V has shown an equal distribution of smokers (about 82 per cent of the patients) and only a slightly higher incidence of hypertension in patients over 52 years of age (33 per cent vs 37 per cent of the patients)

The results of the present study give further evidence to support the relationship between plasma lipid levels and coronary heart disease Furthermore they indicate that prevention or a vigorous treatment of elevated plasma cholesterol and triglycerides may be of value especially in the younger patients

Summary

A possible correlation between the levels of plasma cholesterol and triglycerides and the extent of coronary artery occlusion as determined by angiography was studied in 481 male patients In older patients (over 58 years of age) a pro

nounced coronary occlusion was frequently found at plasma cholesterol levels which could be considered normal for that age while in the younger group (less than 48 years of age) extensive occlusive disease was mainly seen in the presence of elevated plasma cholesterol levels The correlation between plasma triglyceride levels and coronary occlusion seemed to be less pronounced than was the case with plasma cholesterol levels However in patients with low cholesterol levels an increase of plasma triglycerides was associated with more severe occlusive disease

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Epidemiology of coronary heart disease among young army males of World War II

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It seems likely that important epidemiologic factors associated with coronary heart disease (CHD) may be more readily detected in young men with early onset of CHD than in older men with more gradual development of this disease Clinically apparent coronary disease in young adults is relatively infrequent so that most epidemiological studies which reflect its age incidence in the population include very few young cases To obtain a roster of unselected cases of this disease occurring at young ages we employed admissions for CHD among Army personnel serving in World War II An earlier report presented results of a diagnostic review of these cases and data on survival in relation to the review diagnosis and demographic factors [1] Survival in relation to socioeconomic factors had also been evaluated [2] The present epidemiologic study is based on that portion of the original roster for which CHD could be confirmed on diagnostic review and for the sudden deaths in the roster Characteristics of these CHD cases have been compared with those of matched control cases chosen from some Army population in order to identify factors differentiating the two groups Although the information available in the military records was not originally recorded for the purpose of epidemiologic studies it provides valuable observations on factors particularly relevant in CHD

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Methods

A sample of 2,234 *first* Army hospital admissions for CHD from July 1943 through December 1944 was obtained from the Office of the Surgeon General Information in the clinical records of these admissions including electrocardiographic tracings, was subjected to a systematic independent review in order to confirm and explicate the diagnosis The criteria and results of the review have been described [1] Two reviewers both classified 1,297 of the cases as some form of definite or probable CHD In addition there were, in this sample 128 men deceased on arrival at the Army hospital, diagnosed with CHD on that admission who could not be definitely confirmed according to the review criteria Except for six of these cases the available information produced no evidence against the Army hospital diagnosis and the sudden deaths have, therefore, been included here

Controls to be matched with the above cases were obtained using records of the National Service Life Insurance About 98 per cent of men in service during World War II were enrolled in this insurance program and a stratified random sample of the file of premium records was employed as the source of controls Cases and controls were matched on an individual basis forming pairs of comparable age, date of entry into service and with the date of separation of the control later than that of the case In the matching procedure it was impossible to find controls satisfying the selection criteria for 32 cases The latter cases

have been excluded, and consequently the sample for this study consists of 1 393 case control pairs

Distribution of the sample by age race rank and sample status is shown in Table I The median age of the cases is 39 6 years Of the black enlisted cases 56 were re matched to black enlisted controls to determine which of the relationships observed in the total group would appear in the matched black case control pairs A comparable re matching was carried out for 607 white officers who were paired with white officer controls if not already so matched in the sample of 1 393 cases We approached the data in two phases First in the total sample cases were compared to controls matched regardless of rank or race Second, we evaluated that part of the ma r sample where white enlisted cases matched white enlisted controls and also evaluated the matched white officer and matched black enlisted samples to determine whether the same case control differences appeared as were noted in the total sample

Comparable data on cases and controls have been abstracted for periods from military service records according to a uniform format. Information from records of induction or of the first enlistment was obtained to determine date of entry into service residence at induction education, place of birth and race Information on occupation marital status anthropometric measurements pulse blood pressure and medical defects at induction was obtained from this source if induction or if the first enlistment occurred less than four years prior to the date of the hospital admission of the case For longer periods the records of the re enlistment nearest to the three year point but not less than one year before the reference hospital admission were used. Blood group and religion were ascertained from any available records except those from the reference hospitalization of cases Other data abstracted were the last efficiency rating one year prior to the date of hospitalization and grade at the time of the hospital admission From service medical records, information was obtained on service hospital admissions prior to the date of the CHD attack of the case so that all case control diagnostic comparisons cover the time period from induction up to but not including the coronary event. Since all information on the cases and on the controls referred to time

Table I Number of men by year of birth rank and race by sample status

Year of birth	*Age at first hospital admission**	*CHD cases*	*Controls*
1920 1924	21 25	15	16
1915 1919	26 30	64	63
1910 1914	31 35	193	192
1905 1909	36 40	411	416
1900 1904	41 45	265	255
1895 1899	46 50	236	240
1890 1894	51 55	137	140
1885 1889	56 60	59	57
≤ 1884	≥ 61	13	14
Total		1 393	1 393
Rank			
Officer		609	443
Enlisted		768	938
Unknown		16	12
Total		1 393	1 393
Race			
White		1 335	1 300
Black		58	93
Total		1,393	1 393

* Age groups are based on 1944 as year of admission The actual period covered by admissions is July 1943 to December 1944

periods preceding the coronary event of the case it cannot be affected by biases associated with the reference hospitalization

Data have first been analyzed using methods appropriate to case control pairs [3] and estimates of relative risk were obtained that are appropriate for matched case control studies [4] In this analysis it became apparent that within pair correlations are very low and almost no gain is realized by the more precise matched pair technique Therefore we have also resorted to the more conventional methods of estimating relative risk in retrospective studies[5] and to multivariate methods to evaluate effects of intercorrelations between variables and the independent contribution of each variable to the risk of coronary disease [6] In the latter analysis a stepwise multiple regression approach was used in which the case control classification served as the dependent variable For independent variables represented by direct measurements such as height, the actual values were used. Attribute data were transformed so that for each such independent variable the logarithms of case control ratios were assigned to the different classifications on the attribute

Table II Per cent with specified characteristic, relative risk, significance of difference and number with no information among 1 393 male CHD cases and matched controls

Characteristic	*Per cent*		*Relative risk**	*P of test†*	*Number with no information*		*Pairs with full information*
	Cases	*Controls*			*Cases*	*Controls*	
Rural birthplace	30 5	36 4	0 76	< 02	302	356	817
Rural induction residence	11 6	15 4	0 71	< 02	151	170	1 091
Residence in Middle Atlantic states	27 6	22 3	1 33	< 002	2	1	1 390
Some graduate education	18 1	10 5	2 01	< 001	5	4	1 384
Married at induction	59 9	51 3	1 60	< 001	0	3	1 390
Officer	44 3	32 3	2 20	< 001	16	12	1 369
Jewish religion	9 6	4 0	2 61	< 001	111	100	1 193
Heavy frame	25 4	18 8	1 46	< 001	118	150	1 171
Blood group A	47 1	34 5	1 64	< 001	523	305	747
Outdoor active occupation	14 6	21 1	0 64	< 001	215	203	1 111

For matched case-control studies, see reference 4
†Two sided for matched samples

Results

In the comparison of all CHD cases and matched controls the attribute variables which showed statistically significant (P < 0 05, two sided) differences on matched pair tests of significance are presented in Table II For some variables, information was not always available in the service record for both cases and controls and therefore the number with no information is also shown in Table II Percentages are computed using only case control pairs with information available for both members

Higher relative risk of CHD is found for men with the following attributes *residence in the Middle Atlantic states* some *graduate education* *married at induction* of *officer rank* of *Jewish religion* of *heavy frame*, and of *blood Group A* than in those without these traits *Lower relative risk of CHD* is found among those *with rural place of birth or induction* and in *outdoor occupations with high physical activity* No significant differences in risk were noted with differences in pulse, pulse pressure, with service component (Regular Army, selectee, enlistee, etc), or with efficiency rating

Measurement data were analyzed by means of the matched pair t test and the variables which showed significant differences are presented in Table III The *CHD patients* tended to be *shorter heavier* with *greater chest circumference* *higher blood pressure* and *exceeded their standard weight* more than the controls The *socioeconomic status score* as determined from a census classification of occupation and education,[7] was *greater among cases* than among controls. One aspect of the occupational classification requires special consideration In the total sample, among the cases 13 1 per cent and among the controls, 4 3 per cent were classified as physicians, and this produces a relative risk of 3 37 (P < 0 001) Professional technical and kindred occupations other than physicians constituted 14 7 per cent of the cases and 14 1 per cent of the controls yielding a relative risk of 1 05, which was not significantly different from one In the officer matched sample, among the cases 29 8 per cent and among the controls 16 6 per cent, were classified as physicians This produces a relative risk of 2 12 (P < 0 001) When physicians are excluded 35 8 per cent of the cases and 29 0 per cent of the controls are officers with a relative risk of 1 36 (P < 0 001) In the main sample, farmers and farm laborers have a relative risk of 0 54 (P < 0 008), operative and kindred workers, 0 74 (P < 0 005) and laborers except farm and mine 0 71 (P < 0 04) Significant differences in the relative risk of these latter occupations were not found in the white enlisted matched sample or in the officer matched sample

Availability of some items of information par

Table III. Mean values of measurement significance of difference of means and number with no information among 1 393 male CHD cases and matched controls

Measurement	Mean		P of difference	Number with no information		Pairs with full information
	Cases	Controls		Cases	Controls	
Socioeconomic score†	63 7	56 6	< 001	18	14	1 361
Height (inches)	67 7	67 9	< 03	11	22	1 360
Weight (pounds)	164 5	157 2	< 001	11	23	1 359
Chest circumference inspiration (inches)	39 6	38 6	< 001	22	44	1 327
Chest circumference expiration (inches)	36 7	35 7	< 001	22	43	1 328
Blood pressure systolic (mm. Hg)	129 7	128 3	< 02	233	304	978
Blood pressure diastolic (mm. Hg)	81 7	79 9	< 001	233	304	978
Ratio of actual to standard weight (× 100)	112 0	106 6	< 001	11	23	1 359

*Two-sided, for matched samples
†Arbitrary units 1 99 Mean = 60 S D = 27

ticularly of blood group was related to record management procedures and these in turn were affected by rank and possibly race Therefore the findings presented in Tables II and III have been verified by comparing 525 cases matched to controls in the white enlisted sample For variables not strongly correlated with socioeconomic status findings were similar to those of the first analysis although in this instance the data were evaluated as though matched pairs had not been used. For this sample of enlisted cases matched to enlisted controls the relative risk of rural place of residence was 0 74 of Jewish religion 1 46 of heavy frame 1 47 (P < 0 02) and of blood Group A 1 78 (P < 0 001) The differences for Jewish religion are not significant For rural residence the differences are not significant on the classification used, but on another classification based on post office address a significant difference with a comparable risk ratio was obtained in this sample (P < 0 001) There also were significant differences between the white enlisted cases and controls in height (P < 0 006) weight (P < 0 001) and chest circumference (P < 0 001) in the same direction as in the total sample

To take full advantage of the unusual age distribution of this sample the analyses described above were also carried out using only the 688 cases who were 39 years of age or younger at first admission and their age matched controls For the attributes in this analysis the following relative risks similar to those presented in Table II were obtained

Rural birthplace	0 67
Rural induction residence	0 68
Residence in Middle Atlantic states	1 51
Some graduate education	2 32
Married at induction	1 34
Officer	2 17
Jewish religion	2 05
Frame	1 74
Blood group A	1 78
Outdoor active occupation	0 69

All of the above case control differences were significant on statistical testing (P < 0 05) Measurement data also were evaluated for cases less than 40 years of age at admission and their controls Mean case control differences of the same sign and similar magnitude as shown in Table III were noted in the under 40 group and they all were statistically significant (P < 0 01) However the mean socioeconomic score of both groups was considerably lower (49 9 cases 47 0 controls) and mean weight was slightly lower (163 1 cases, 154 2 controls) in the younger age group

Many of the variables listed in Tables II and III are correlated, and to evaluate their independent contributions a stepwise multiple regression

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Availability of some items of information par

by means of the stepwise regression analysis in which white officer cases were matched to white officer controls. This analysis selected as having significant ($P < 0.05$) partial correlations the same variables for all diagnoses combined as those that were selected in the total group presented in Table IV except for the urban rural classification The partial correlation coefficient of the latter variable failed to reach the specified level of significance in the officer officer analysis For the MI CO and CT group in that analysis the same variables were selected as are presented in Table IV for these diagnoses except that the ABO blood group did not attain a significant partial correlation coefficient. The number of AP and CI cases in the officer officer stepwise regression analysis was only 176 and only occupation group religion and ratio of actual to standard weight attained significant partial coefficients

Despite the small number of blacks in the race matched sample significant differences in the same direction as in the total sample were obtained for the measurement of chest circumference on expiration The mean chest circumference on expiration was 35 6 inches for cases and 34 6 inches for controls ($P < 0.05$)

The military medical experience of cases prior to their hospital admission for heart disease was reviewed and compared with the medical experience of the controls for the same time period No significant differences were noted in either individual diagnoses or diagnostic groupings of particular interest in coronary disease epidemiology

Discussion

It seems likely that factors important in the epidemiology of CHD might be detected more readily in persons with early onset of the disease Clinically apparent disease in young adults is infrequent and most epidemiologic studies of the disease reflect its age incidence in the population and include very few young cases Military personnel in World War II represent a unique resource in that the disease experience of a very large group of young men was being monitored under conditions favorable for early detection of the disease and with standardized documentation of diagnosis and treatment. Army administrative records make possible an enumeration of the entire group at risk during World War II and thus provide a means of selecting control samples of known representativeness matched to the cases on variables that, if uncontrolled, might confound the case control comparison

The literature on the epidemiology of coronary disease concerns itself with a multitude of factors[8,9] yet the relative importance of these factors requires further clarification and refinement. The present study comparing characteristics of 1 393 first hospitalizations for CHD in young Army men and age matched controls has confirmed some generally recognized risk factors and revealed others with provocative implications. Except for occasional missing records or wrong identifications these cases were essentially consecutive admissions for CHD during the 18 month period of study and they showed significant differences from their matched controls in the standard clinical variables of systolic blood pressure diastolic blood pressure, weight, and ratio of actual to standard weight In addition, the CHD cases had a greater chest circumference had a heavy frame and were slightly shorter than were the matched controls. Other characteristics associated with a *significantly higher* risk of CHD were residence in the Middle Atlantic States a higher socioeconomic score some graduate education being married at induction being an officer being of Jewish religion and having blood Group A A *significantly lower* risk of CHD was found for the characteristics of rural birthplace for rural induction residence and for preservice occupations outdoors requiring high physical activity Relationships of the same direction and essentially the same magnitude were found among cases age 39 years or less when compared to their age matched controls.

Since special efforts were made to establish matched controls representative of the Army population of the same age and the same period of entry into service as the cases the emergence of these significant differences between cases and controls is probably not due to artifacts of methodology and some of these true differences may be of biologic importance It is likely that both constitutional and environmental influences are being reflected in the list of factors identified in this study Constitutional possibly genetic influences are suggested by the findings of significant differences in height frame chest circumference and blood group The higher incidence of coronary heart disease found for men of Jewish

Table IV Simple, partial, and multiple correlation coefficients obtained in stepwise multiple regression analysis of CHD case control classification as dependent variable by diagnostic classification white male case control pairs

Variable	Correlation		
	Simple	*Partial*	*Multiple*
Total (N = 2 494)*			
Occupation group	0 22	0 22	0 22
Deviation from standard weight	0 18	0 16	0 27
ABO blood group	0 12	012	0 29
Blood pressure diastolic	0 14	0 12	0 32
Height	−0 06	−0 07	0 32
Chest circumference insp	0 17	0 08	0 33
Urban rural classification	0 11	0 06	0 34
Religion	0 11	0 05	0 34
Myocardial infarction, coronary occlusion and coronary thrombosis (N = 1 246)*			
Chest circumference insp	0 19	0 19	0 19
Blood pressure diastolic	0 18	0 16	0 24
Urban rural classification	0 11	0 11	0 27
Height	−0 07	−0 09	0 28
Occupation group	0 12	0 10	0 29
ABO blood group	0 09	0 08	0 30
Angina pectoris and coronary insufficiency (N = 654)*			
Occupation group	0 30	0 30	0 30
ABO blood goup	0 17	0 19	0 35
Chest circumference insp	0 18	0 17	0 38
Height	−0 06	−0 12	0 40
Religion	0 18	0 09	0 40

Under the hypothesis of zero correlation the sample estimates r shown in the table below have the P values indicated in the columns

N	P = 0 05 r =	P = 0 01 r =	P = 0 001 r =
2 494	0 04	0 05	0 07
1 246	0 06	0 07	0 09
654	0 08	0 10	0 13

analysis was carried out This technique selects the variable most strongly related to the case control classification and then one by one introduces additional variables which at that point produce the greatest reduction in the residual sum of squares The stepwise multiple regression analysis was carried out only on white cases and controls, disregarding the matched pair relationship It was carried out separately for the total CHD sample and for subgroups based on the review diagnosis of myocardial infarction coronary occlusion coronary thrombosis (MI CO and CT) and of angina pectoris and coronary insufficiency (AP and CI) Table IV shows for each diagnostic group those variables with significant ($P < 0.05$) partial correlation coefficients in the sequence in which they were selected by the stepwise regression technique *In all three analyses* of total CHD of MI, CO, and CT, and of AP and CI *significant partial correlations with the case control classification* were obtained for *occupation group ABO group, chest circumference on inspiration and height* Diastolic blood pressure and the urban rural classification appeared in the total group and in the MI, CO and CT group Religion appeared to have a significant partial correlation in the total group and in the AP and CI group Ratio of actual to standard weight appeared in the total group only For the same number of variables selected in the stepwise regression the multiple correlation coefficient in the AP and CI group was somewhat greater than in the MI, CO, and CT group, and the difference is significant ($P < 0.02$)

In an attempt to control for the effect of differences in rank, another sample was analyzed

members were white enlisted men The relative risk of Group A in this comparison was 1 8 (P < 0 001) Even though any source of information on blood group was accepted in abstracting the service records for cases the grouping was done before the coronary event and most of the men were grouped well before they could have shown any signs or symptoms of coronary disease. Thus these data give very strong support to the increased risk among individuals with Group A blood.

The stepwise regression analysis illuminates some of the epidemiologic differences between the different forms of coronary disease Essentially the same variables were selected as significant for the MI CO and CT group as for the AP and CI group but with a different emphasis For the MI CO and CT cases the regression program identified chest circumference and diastolic blood pressure as the two most significant variables For the AP and CI cases the most significant variables were occupation group and ABO blood group After five variables had been entered the multiple correlation coefficient in the MI CO and CT group was 0 29 while for the AP and CI group after five variables it was 0 40 It, therefore appears that angina pectoris is more highly predictable from identifiable risk factors than are the first manifestations of myocardial infarction or death from CHD However the similarities in the outcome of the multiple regression analyses for the two diagnostic groups are more impressive than the differences

The very small number of CHD cases among the blacks reflects partly Army policies during World War II regarding induction of blacks and partly racial differences in the incidence of the disease Racial differences in morbidity from CHD are strongly age dependent and are well documented.[25] Our data lead to an estimate of relative risk for black males of 0 61 (P < 0 005) Although the group is very small it is of interest because different etiologic factors might affect blacks than affect whites. Even in this small sample it has been possible to demonstrate that body build is of epidemiologic significance for both groups

Information on cigarette smoking and serum cholesterol was not entered in Army records of the period covered by this study consistently or in a manner comparable for cases and controls Thus these factors could not be evaluated in our investigation Including this information in the multivariate analysis very likely would have resulted in even better predictability of CHD as indicated by higher multiple correlation coefficients. Also the relative importance of some of the factors studied in distinguishing cases from controls might be affected by including smoking and cholesterol as variables in the multivariate analysis The absence of data on these variables in this study only reflects their unavailability

Summary

An epidemiologic study was carried out on 1 393 cases of CHD in World War II Army men median age 39 6 years by comparing these cases with representative age matched Army controls using data from military records of both groups, particularly records of induction into service

Factors showing significant (P < 0 05) association with the development of angina pectoris coronary insufficiency myocardial infarction and death from CHD at this young age were higher systolic and diastolic blood pressure higher weight and ratio of actual to standard weight, aspects of body build as measured by a greater chest circumference a heavy frame and being shorter than the matched controls.

Other characteristics more prevalent among the coronary cases than among the matched controls and therefore associated with a higher risk of CHD were geographical residence in the Middle Atlantic States a higher socioeconomic score some graduate education being an officer being of Jewish religion and having a blood Group A

A significantly *lower* risk of CHD was found for rural birthplace and previous outdoor occupation requiring high physical activity Men whose previous occupation was that of a farmer or farm laborer had a relative risk of 0 54 (P < 0 008) compared with other occupational groups Stepwise multiple regression analysis revealed the successive contribution to risk of first myocardial infarction coronary thrombosis and coronary occlusion associated with size of chest circumference level of diastolic blood pressure urban rural classification height (negatively associated) occupational group and ABO blood group This analysis evaluates the contribution of each selected factor independent of the factors selected in previous steps. Similar multiple regression analysis applied to angina pectoris and coronary insufficiency cases identified occupa

religion and the low incidence in black Army men in this study add support to the preceding indications for a constitutional component in CHD in young adults Lipoprotein phenotyping had not yet been discovered when these cases had their first hospital admission, however, it is likely that the prevalence of typable forms of hyperlipoproteinemia would also be higher among the cases than among the matched controls.

Other findings in this study warrant comment. Mortality from coronary disease shows clear variation with geography similar to the variation in morbidity found in our data [10] The urban rural differences found by us have also been noted by others [11,12] The urban rural classification is correlated with many social and economic factors which even among veterans distinguish the urban and rural life styles [13] and probably also reflects variables such as physical activity lipid levels smoking or as yet unknown influences In the multiple regression analysis the urban rural continuum was found to have a relationship to coronary disease independent of occupation body build blood group and blood pressure but we cannot provide meaningful information on the covariance of additional factors

Occupation and education were found to be strongly related to each other and to coronary disease and although in the stepwise multiple regression analysis occupation was selected in preference to education as the determining factor, that selection is somewhat arbitrary Part of the relationship to coronary disease may be mediated by physical activity in occupation which in this study had a significant negative association with coronary disease Others[14,15] have reported that behavior characteristics and personality type have an epidemiologic significance in CHD In our study we could not demonstrate a definite relationship between the case control classification and the efficiency rating of officers obtained from military records The latter rating probably constitutes a global evaluation of function under the very unusual circumstances of service in World War II and, therefore, it is not comparable to the specific test instruments generally employed in the evaluation of personality or behavior type

Married men are commonly reported to have a lower risk of coronary disease than those who are single, divorced, or separated[16], however in the total sample we found a higher relative risk

Marital status in this study was determined at time of induction or enlistment or, if entry into service was more than four years before the coronary event, at re enlistment. Since the sample is matched on age that variable is not producing the unexpected finding of a higher risk for married men The multiple regression analysis did not identify marital status as having a significant partial correlation with coronary disease In the sample matching officer cases to officer controls the relative risk of the married group was 0 97 and no significant difference was found between married men and those of other status when data for the sample matching white enlisted cases to white enlisted controls were analyzed. Thus the findings in the main sample probably are related to an association of marital status and military rank

Ethnic factors have been reported to be associated with coronary disease [17] In the stepwise multiple regression analysis for all coronary diagnoses combined the scaling of Protestant, Catholic or Jewish religion has a small but significant partial correlation coefficient after the effect of occupational and geographic variables has been corrected for In the sample matching officers to officers the relative risk of those with Jewish religion was 3 2 (P < 0 001)

Anthropometric measurements have been reported to be associated with CHD [18-20] In our stepwise multiple regression analysis the variable selected first was ratio of actual to standard weight which already includes a correction for height Despite this height had a significant partial correlation coefficient after the association of the weight ratio to CHD had been accounted for Body build probably reflects an interplay of various genetic and environmental factors some of which are clearly related to coronary disease

The ABO blood group has been reported to be associated with a wide variety of diseases[21] and an increased risk of CHD among Group A and Group A 1 individuals has been reported [23] The accuracy of the ABO system determination during World War II has been evaluated[24] and was found to be 91 per cent Data on blood group generally are not now available in military records of commissioned officers, which explains why this information could not be obtained for 523 cases and 305 controls of whom 486 and 285 respectively were officers We evaluated the relationship in 525 case control pairs in which both

A simple, rapid method for the diagnosis of first-degree sinoatrial block in man

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During the past ten years there has been widespread interest in cardiac conduction defects in man One major cause for this intense interest has been the availability of temporary and permanent cardiac pacing to treat these conditions. Pacing techniques broaden the clinician s therapeutic horizons because they can be used not only as primary treatment for S A or A V block or arrhythmias but also in combination with cardioactive drugs to control difficult arrhythmias or manage cardiac failure in patients with A V block For the past five years, recording His bundle depolarization in intact awake man using catheter electrodes has been used to identify the site of A V block Epidemiologic studies using this technique will provide information which will almost certainly improve our management of A V block and its precursers. Until very recently we have been less fortunate in our ability to test the functions of the S A node in man It is the purpose of this communication to describe a simple method for diagnosing first degree S A block i.e , delay of conduction from the S A node to the atrium This technique can be useful clinically to evaluate intermittent disorders of S A conduction

In 1962 Langendorf and co workers[1] analyzed a recording from a patient who had atrial parasystole Atrial activation by the parasystolic focus elicited a variety of interesting responses which allowed this group of investigators to infer some of the functional characteristics of conduction between the S A node and the atrium in their case Based on their observations, we developed an analytic technique for estimating the conduction time between the S A node and atrium in man and have used it to diagnose first degree S A block in humans[2,3] Our full analysis is laborious, and thus more appropriate to the research laboratory than to routine clinical practice At this time we would like to report a simpler analysis which can be quickly applied in clinical practice

The main features of our analytic method are shown in Fig 1 Atrial premature depolarizations (A_2) are elicited by a brief electrical pulse introduced via a right atrial catheter every tenth spontaneous atrial cycle or so using an ordinary fixed rate pacemaker Trace 1 shows four consecutive spontaneous atrial depolarizations (A_1) in sinus rhythm which have a constant cycle length (A_1A_1) of 1 0 second. Six test cycles (A_1A_2) and the subsequent return cycle (A_2A_3) are shown in traces 2 through 7 the A_1A_2 interval is shortened in 0 1 second intervals from 0 9 to 0 4 second. In traces 2 and 3 the sum of A_1A_2 and A_2A_3 equals two spontaneous sinus cycles ($A_1A_2 + A_2A_3 = 2\ A_1A_1$) i e the return cycle is fully compensatory This fully compensatory pause indicates that the sinus node was not reset i.e A_2 did not traverse the perinodal fiber zone[4] to depolarize the sinus node before it spontaneously depolarized[2,3] Traces 4 through 7 show that although A_1A_2 is shortened over a wide range the return cycle A_2A_3 is constant at 1 2 seconds The constancy of A_2A_3 suggests not only that the sinus node has been depolarized and reset by A_2 but also that the returning sinus cycle is unperturbed (the same as in normal sinus rhythm) and that conduction from atrium to

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tional group ABO blood group, size of chest circumference, height (negatively associated), and religion as independent contributors for risk of this manifestation of CHD at a young age

We gratefully acknowledge the work of Dr Thomas W Mattingly former Chief of Medicine and Cardiology Walter Reed Army Medical Center Washington D C who served as an independent reviewer of the clinical histories and electrocardiograms for this study The conduct of this work depended on medical and other records of the Department of Defense the Veterans Administration and the National Archives and Records Service General Services Administration We are indebted to those agencies particularly their records management personnel for the ready access they generously provided to the required material The records operations were carried out by the operations staff of the Medical Follow up Agency under the direction of Mr A Hiram Simon records abstracting and coding was done under the direct supervision of Mrs. Vivian Farley and Mr Thomas Preston assisted with data processing.

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causes inconvenience We think that many cardiologists will find this technique useful to evaluate sinus node function in individuals with intrinsic disease of the S A node or drug induced functional abnormalities of the node

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Table I Estimation of conduction time between S A node and atrium

Trace No.	A_1A_2 *(seconds)*	A_2A_3 *(seconds)*	$A_1A_2 + A_2A_3$ *(seconds)*
2	0 9	1 1	2 0
3	0 8	1.2	2 0
4	0 7	1 2	1 9
5	0 6	1.2	1 8
6	0 5	1 2	1 7
7	0 4	1 2	1 6

Note that since the cycle length of sinus rhythm 1 0 second, $A_1A_2 + A_2A_3$ is always 2.0 seconds when A_2A_3 is fully compensatory When the sinus node is reset by the propagation of A_2 into the sinus $A_1A_2 + A_2A_3$ becomes less than 2.0 seconds.

sinus node and sinus node to atrium are approximately equal [2,3] If this were not so, A_2A_3 would be more variable in traces 4 through 7

Using the responses from the portion of the atrial cycle during which sinus node reset is obtained allows estimation of the conduction time from S A node to atrium The A_1A_2 and A_2A_3 intervals are measured and listed in two columns (Table I) in descending order of the A_1A_2 intervals It is clear from these lists when the return cycle (A_2A_3) becomes constant. Conduction time from S A node to atrium is then obtained from the following relationship

$$\text{Conduction time from S A node to atrium} = \frac{\text{Average } A_2A_3 \text{ Interval} - \text{Average } A_1A_1 \text{ Interval}}{2} =$$

$$\frac{1\ 2 - 1\ 0}{2} = 0\ 10 \text{ sec}$$

Although norms are still being established for this interval, it is usually considerably less than 0 12 sec and larger values are considered abnormal When S A conduction is very prolonged, A_2A_3 may be fully compensatory no matter how early A_2 is introduced, i e , A_2A_3 continues to prolong as A_1A_2 is shortened.

When spontaneous APD's are analyzed by this method, abnormalities of conduction between sinus node and atrium can sometimes be detected If a spontaneous A_2 is very early, e g , $A_1A_2 = 0\ 32$ sec when the atrial cycle (A_1A_1) is 0 80 sec and the return cycle is 1 50 sec , one can suspect that conduction is delayed in the perinodal tissues Caution should be exercised in analyzing spontaneous A_2's, however, because the range of A_1A_2 intervals available is often narrow, limiting the analysis For example, the return cycle of 1 50 sec. just mentioned could be due to a lengthening of the sinus node cycle following depolarization of the sinus node by A_2 This possibility is not likely when the A_2A_3 interval is constant over a wide range of A_1A_2 intervals

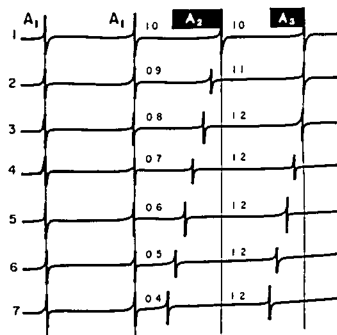


Fig 1 Seven selected test (A_1A_2) and return (A_2A_3) cycles a premature atrial depolarization was elicited with an electrical stimulus every tenth spontaneous atrial cycle recordings of the atrial electrogram are shown

We have found measurement of conduction time from SAN to atrium useful in evaluating (1) patients with sinus bradycardia and syncope or other central nervous system symptoms and (2) patients who have recovered from second degree S A block which is attributed to drugs or intercurrent illness In such instances, residual first degree S A block can be detected Analysis is difficult to apply when sinus arrhythmia is marked, but this difficulty only occasionally

polyethylene catheter and a P23AA pressure transducer

Results

The control heart rate was the same under both types of anesthesia as illustrated in Fig 1 The control heart rate in denervated animals was significantly greater than that in innervated animals ($p < 0.001$) under both types of anesthesia

Fig 2 illustrates the effects of different anesthetic agents on the toxicity of ouabain Bilateral sinus and vagus nerve section decreased the toxic doses of ouabain under both types of anesthesia ($p < 0.001$) Ouabain toxicity is greater in animals anesthetized with chloralose urethane When compared with the corresponding doses in animals anesthetized with pentobarbital sodium both the dose of ouabain required to produce ventricular tachycardia and the lethal dose were significantly smaller in animals anesthetized with chloralose and urethane ($p < 0.001$)

The relationship between the dose of ouabain required to produce ventricular tachycardia and the lethal dose was the same under both types of anesthesia In innervated animals anesthetized with pentobarbital the dose of ouabain required to produce ventricular tachycardia was 78 8 ± 1 5 per cent of the lethal dose in animals anesthetized with chloralose urethane the arrhythmic dose was 78 0 ± 2 7 per cent of the lethal dose Denervation significantly decreased the arrhythmic to lethal dose ratio to 0 68 ± 0 03 in animals anesthetized with pentobarbital ($p < 0.01$) Although the arrhythmic dose was a smaller fraction of the lethal dose in denervated animals anesthetized with chloralose urethane 0 71 ± 0 05 this value was not significantly different from that obtained for innervated animals under chloralose urethane anesthesia

The effect of different anesthetic agents on acetylstrophanthidin toxicity is shown in Fig 3 As was the case with ouabain denervation increased the toxicity of acetylstrophanthidin under both types of anesthesia However unlike the results obtained with ouabain the toxic doses of acetylstrophanthidin were not affected by the type of anesthetic agent used.

The relationship between the dose of acetylstrophanthidin required to produce ventricular tachycardia and the lethal dose in

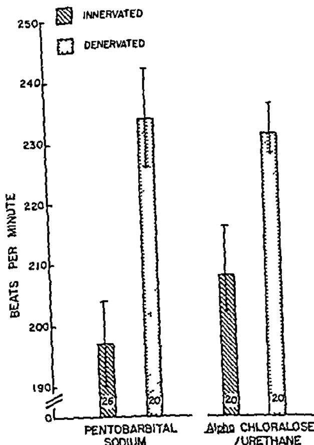


Fig 1 Heart rates in cats immediately before the intravenous infusion of either acetylstrophanthidin or ouabain was begun Under each type of anesthesia the difference between innervated and denervated animals is statistically significant, $p < 0.001$

animals anesthetized with chloralose and urethane (innervated, 54 3 ± 3 4 per cent denervated, 56 7 ± 2 7 per cent was the same as that which occurred in animals anesthetized with pentobarbital (innervated, 59 1 ± 4 1 per cent denervated, 58 5 ± 3 4 per cent) The arrhythmic to lethal dose ratio for acetylstrophanthidin is significantly less than the same ratio for ouabain ($p < 0.001$) Denervation altered the toxic dose relationship of ouabain in animals anesthetized with pentobarbital but had no effect on this relationship of acetylstrophanthidin in cats anesthetized with pentobarbital

Discussion

The toxicity of digitaloid substances can be determined in several ways The relationship between the dose of digitalis required to produce ventricular tachycardia (arrhythmic dose) and

The effect of different types of anesthesia on digitalis toxicity*

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Most general anesthetic agents have significant effects on the circulation [1] In addition to producing direct and reflex changes in the activity of the cardiovascular system these agents can modify cardiovascular responses to specific physiologic interventions[2] as well as cardiovascular responses to drugs [3-5] The pharmacological actions of all general anesthetics are not identical [1] Therefore, it is not surprising that the type of anesthesia to which the animal is subjected plays a role in determining the cardiovascular changes produced by drugs[5] and by physiological manipulations [2]

The cardiac toxicity of digitalis substances is often studied in anesthetized animals The present investigation was undertaken in order to determine whether or not the development of digitalis induced cardiac arrhythmias in cats is influenced by the anesthetic agent used. Digitalis toxicity was studied in animals anesthetized with either pentobarbital sodium or a combination of chloralose and urethane Both types of anesthesia are commonly used in animal studies.

Methods

The experiments were performed on cats of either sex that weighed between 1 8 and 4 0 kilograms Animals in one group were anesthetized with an intravenous injection of α chloralose, 60 mg per kilogram dissolved in urethane, 500 mg per kilogram Animals in the second group were anesthetized with pentobarbital sodium, 35 mg per kilogram, administered either intravenously or intraperitoneally In the innervated ouabain control group, it was shown that the route of administration of pentobarbital had no effect on either of the toxic doses of ouabain (intraperitoneal administration of anesthetic, 9 animals VT = 110 0 ± 15 2 μg per kilogram, LD = 146 9 ± 19 4 μg per kilogram, intravenous administration, 8 animals VT = 112 2 ± 17 8 μg per kilogram, VF = 140 6 ± 24 8 μg per kilogram) Consequently all animals were included in one group No supplemental administration of either type of anesthetic was required during the experiment

The effect of anesthesia on the toxicity of two different digitaloid substances was studied Ouabain was administered by a continuous intravenous infusion at a rate of 2 5 μg per kilogram per minute Acetylstrophanthidin was also administered by intravenous infusion 10 μg per kilogram per minute The infusion solutions were made up for each animal such that the correct dose per minute was contained in a 0 5 ml volume Two endpoints of digitalis toxicity were studied the dose of cardenolide necessary to produce ventricular tachycardia and the lethal dose Ventricular tachycardia was defined as a unifocal ventricular arrhythmia which persisted for at least one consecutive minute The quantitative relationship between the arrhythmic dose (ventricular tachycardia) and the lethal dose was also noted.

The Lead II electrocardiogram and the arterial blood pressure were recorded continuously on a Grass Model 7 polygraph Arterial blood pressure was monitored from a femoral artery with a

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difference in the toxicity of ouabain under the two anesthetic conditions cannot be correlated with a difference in heart rate

Another possible basis for the observed difference in ouabain toxicity in animals anesthetized with chloralose urethane as compared to that in animals anesthetized with pentobarbital is a difference in the activity of the baroreceptor reflexes under the two different types of anesthesia There should be a greater degree of sympathetic nervous system activity in the presence of an anesthetic that depresses baroreceptor activity Under such conditions digitalis toxicity would be expected to be increased Brown and Hilton[12] found that under chloralose anesthesia the baroreceptors were more active than under other types of anesthesia including that produced by barbiturates Digitalis toxicity should be less in animals anesthetized with chloralose and urethane This was not the case in this study There must be additional factors to consider

A disparity in effects on baroreceptors is not the only difference in the pharmacologic actions of pentobarbital and those of chloralose and urethane Pentobarbital decreases vagal tone[13,15] and has only a slight effect on sympathetic outflow during the first hour to hour and a half following induction[5,13,14,16] There is also evidence to suggest that pentobarbital actually inhibits the release of catecholamines from the adrenal medulla[17] On the other hand, chloralose appears to potentiate sympathetic effects[12,18] and urethane has been found to increase the release of epinephrine from the adrenal medulla[9]

Thus, sympathetic activity during pentobarbital anesthesia apparently is less than that during chloralose urethane anesthesia in spite of the fact that baroreceptor reflexes are more depressed during the former It is not surprising that the toxicity of digitalis in animals anesthetized with the former was less than that in animals anesthetized with the latter This pharmacological difference between anesthetics might, therefore explain the finding that the toxic doses of ouabain are smaller in animals anesthetized with chloralose and urethane

The problem yet to be resolved is why acetylstrophanthidin toxicity was not influenced by the type of anesthesia to which the animals were subjected. Perhaps a difference in the pharmacological actions of ouabain and acetyl strophanthidin is the answer There appears to be no direct evidence relating to this question Quest and Gillis[20] compared the effects of acetylstrophantidin and ouabain on sinus nerve activity in cats following injections into the artery that supplies the carotid sinus. Acetylstrophanthidin was found to be more potent in increasing sinus nerve activity

There is indirect evidence that following systemic administration, acetylstrophanthidin produces a greater degree of sympathetic activity than does ouabain In dogs D,L-propranolol increased the dose of acetylstrophanthidin required to produce ventricular tachycardia, but did not alter that dose of ouabain[21] In cats D,L-propranolol increased the lethal dose of acetylstrophanthidin but not that of ouabain[22] Attenuation of β-adrenergic receptor activity had a greater effect on the toxicity of acetylstrophanthidin than that of ouabain in the results just cited. This would be expected if acetylstrophanthidin effects a greater increase in sympathetic activity than does ouabain An additional piece of evidence in favor of this hypothesis was obtained from denervated cats[23] In this preparation afferent nerves from the baroreceptors and efferent vagal fibers have been severed. In such a preparation a drug produces a maximal pressor response because reflex compensation is absent In these animals at the time that ventricular tachycardia developed, ouabain produced no change or a very slight increase in mean arterial pressure over control values At that same point acetylstrophanthidin produced a marked increase in mean arterial pressure over control values[23] An increase in sympathetic outflow effected by acetylstrophanthidin but not by ouabain could account for such a difference

If, in fact, acetylstrophanthidin has a greater ability to increase sympathetic activity than does ouabain the differences observed in this study might be explained in the following manner The ventricular arrhythmias produced by acetylstrophanthidin are the result of a direct action of acetylstrophanthidin on the heart and an indirect action via an increase in sympathetic activity On the other hand the ventricular arrhythmias produced by ouabain are the result primarily although not entirely[24,25] of a direct action of ouabain on the heart. Any condition in

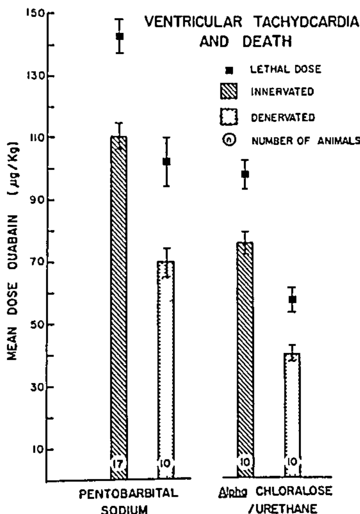


Fig 2 A graphical representation of the dose of ouabain required to produce ventricular tachycardia and the lethal dose of ouabain in animals anesthetized with pentobarbital (35 mg per kilogram) or with chloralose (60 mg per kilogram) urethane (500 mg per kilogram)

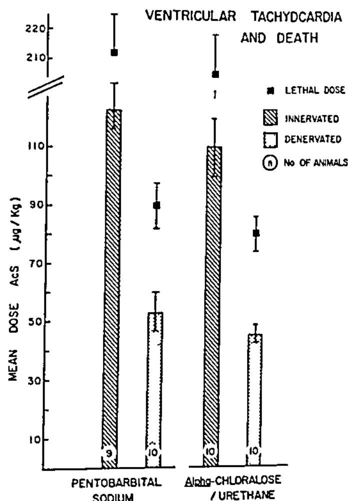


Fig 3 A graphical representation of the dose of acetylstrophanthidin required to produce ventricular tachycardia and the lethal dose of acetylstrophanthidin in animals anesthetized with pentobarbital (35 mg per kilogram) or with chloralose (60 mg per kilogram) urethane (500 mg per kilogram)

the lethal dose is one means of comparing the toxicity of cardiac glycosides [10] In this investigation, the arrhythmic to lethal dose ratio for acetylstrophanthidin was significantly smaller than that for ouabain under both types of anesthesia This measure of toxicity in cats appears to be characteristic for a given glycoside, it is not altered by the type of anesthesia to which the animal is subjected

The amount of digitaloid substance required to produce ventricular tachycardia and that which produces death (micrograms per kilogram) are other criteria for studying digitalis toxicity The type of anesthetic agent used affected the dose of ouabain required to produce ventricular tachycardia and the lethal dose of ouabain, but had no effect on either dose of acetylstrophanthidin In animals anesthetized with chloralose and urethane the toxic doses of ouabain were smaller than those doses in animals anesthetized with pentobarbital

The first problem to be considered deals with the toxicity of ouabain What might account for the differences that were observed? A difference in heart rate under the two different types of anesthesia is a possible explanation Wittenberg and co workers[11] demonstrated that the time required to produce digitalis induced augmentation of automaticity in dogs decreased as the rate at which the heart was being driven was increased The toxicity of digitalis was increased by increasing the heart rate However, in the present investigation, the control heart rates in innervated animals were the same under both types of anesthesia, the same is true for the control heart rates of denervated animals Thus the

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which sympathetic activity is increased, for example chloralose urethane anesthesia, would potentiate ouabain toxicity to a greater extent than acetylstrophanthidin toxicity That is, the increase in sympathetic activity produced by chloralose and urethane is not significant relative to that produced by acetylstrophanthidin, the toxicity of acetylstrophanthidin is not dependent on the anesthetic agent However, chloralose urethane anesthesia increases ouabain toxicity because the increase in sympathetic activity under this condition is significant relative to that change in sympathetic activity produced by ouabain in animals anesthetized with pentobarbital

Summary

This investigation was undertaken in order to determine whether or not the type of anesthetic agent used modified the cardiotoxicity of either ouabain or acetylstrophanthidin Ouabain toxicity was greater in animals anesthetized with chloralose and urethane than it was in animals anesthetized with pentobarbital The toxicity of acetylstrophanthidin was the same under both types of anesthesia It is suggested that these results can be explained by an interplay between differences in the pharmacological actions of the digitaloid substances studied and differences in the pharmacological actions of the anesthetics under question

The results of this study are significant for two reasons They reinforce the importance of carefully choosing an anesthetic agent(s) All anesthetics do not produce identical pharmacological actions Drugs that produce anesthesia can modify an animal's response to other drugs There is a need for more information on the interaction between anesthetics and other drugs This has clinical as well as experimental applicability The differences between anesthetic agents with regard to interactions with catecholamines have been long recognized[26,27] However, there appears to be little information on such differences between anesthetics with regard to other drugs

This study also points out the need for further study of the specific pharmacological actions of different digitaloid substances It appears as though different cardenolides may have different potentials for increasing sympathetic activity With further study, other differences may be found. The existence of differences in the pharmacological actions of different cardiac glycosides should increase the chances of finding a therapeutically useful cardioactive steroid that produces less toxicity than the agents that are currently in use For example the finding of a difference between digitaloid substances in ability to increase sympathetic outflow would improve the possibility of the development of a cardiotonic digitaloid substance that has little ability to increase sympathetic outflow The new compound should have less potential for producing cardiac arrhythmias Such a substance might be expected to be very useful clinically because the margin of safety should be larger than that of a similar compound that produces a significant increase in sympathetic outflow in addition to its direct positive inotropic effects.

The excellent technical assistance of Ms. Janis Hamada and Ms. Nan Evans is gratefully acknowledged. The acetylstrophanthidin used in this study was generously supplied by the Eli Lilly Company

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Table I The pH, Po_2 and Pco_2 of Tyrode solution before and after the addition of various compounds

	pH	*Po_2 (mm. Hg)*	*Pco_2 (mm. Hg)*
Tyrode solution	7 25	600	26
0 5 mM Adenosine	7 16	620	30
0 5 mM AMP	7 20	612	31
0 5 mM ADP	7 15	628	32
0 5 mM ATP	7 19	610	28
2 5 mM Adenosine	7 18	670	31
2 5 mM AMP	7 15	600	29
2 0 mM ADP	7 21	615	31
2 5 mM ATP	6 96	675	29

ring was lowered so that it rested on the septum at the base of the muscle and restrained upward movement of the heart The apex of the muscle was tied to the anode of an RCA 5734 force transducer connected through a bridge to the preamplifier of a Sanborn (Model 8800 03A) or a Brush (Model 220) recorder The muscle length could be adjusted by means of a controlling screw (length adjustment screw Fig 1) The ventricles were driven at a rate of 60 to 75 beats per minute employing square wave pulses of 5 milliseconds duration at a voltage approximately 10 per cent above threshold.

Tyrode solution containing 4 per cent low molecular weight dextran was used for perfusion (150 mM Na^+ 145 mM Cl 4 2 mM K^+ 0 32 mM HPO_4 11 9 mM HCO_3 0 49 mM Mg^{++} 1 8 mM Ca^{+} and 5 5 mM dextrose) The solution was equilibrated with a 97 per cent O_2 + 3 per cent CO_2 gas mixture The pH, Po_2 and Pco_2 of the Tyrode solution before and after addition of various adenine nucleotides are shown in Table I The osmolarity of the solution after the addition of 4 per cent low molecular weight dextran was 274 mOsm per liter The temperature ranged between 23 C and 27 C in this series of experiments, but did not vary by more than ± 0 5 C in any one experiment.

In all experiments a control record of at least 10 minutes duration was obtained before each stage of the study to establish a steady state of force development. The control state as referred to in this investigation is that in which the muscles were being perfused with oxygenated Tyrode solution and were contracting isometrically at just below the peak of their length active tension curve The developed force was measured as the

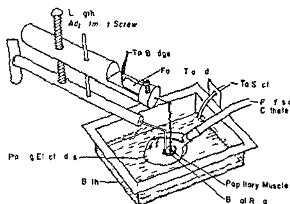


Fig 1 Diagrammatic representation of the mounted isometrically contracting in situ right ventricular papillary muscle of feline heart.

difference between the peak systolic force and the diastolic force The muscle diameter was measured by an ocular micrometer and force was calculated in grams per square millimeter of the average cross sectional area of the muscle The muscle diameter varied from 0 5 to 2 5 mm in our studies The resultant force secondary to the changes in the perfusate is reported as per cent of control force

When viewed through the dissecting microscope the muscle does not appear to shorten when it contracts This isometrically contracting papillary muscle is an ideal preparation for observing changes in developed force secondary to changes in the perfusate since it is perfused through the coronary vessels. In our studies change in force occurred rapidly following a change in the perfusate usually within 30 to 60 seconds The control force developed by these muscles varied from 1 0 gram per square

Effects of adenine nucleotides on contractility of normal and postischemic myocardium*

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Rapid deterioration of myocardial contractility occurs when heart muscle is subjected to hypoxia and ischemia [1-4] Several investigators[5-8] have reported diminished stores of creatine phosphate (CP) and adenosine triphosphate (ATP) in hypoxic failing hearts. In skeletal muscle, it has been shown that ATP is the immediate source of energy for contraction and is rapidly replenished by CP hydrolysis [9] Recent work on isolated cardiac muscle suggests that CP hydrolysis may operate in a similar manner to replenish the ATP used in myocardial contraction [10] If ATP is the immediate source of energy for contraction, the deterioration in the mechanical function of ischemic hearts may to a certain extent, be causally related to the depletion of high energy phosphates We investigated the effect of adenine nucleotides on the force development of normal and postischemic myocardium

From the Cardiology Section and Cardiopulmonary Laboratory New York Veterans Administration Hospital New York the Department of Medicine New York University School of Medicine New York and the Department of Physiology Downstate Medical Center State University of New York, Brooklyn This investigation was supported by the New York Heart Association and the United States Veterans Administration

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*** Dr Fisher was a Clinical Investigator of the United States Administration during the period covered by the study

Methods

The preparation used was the isometrically contracting feline right ventricular papillary muscle which remained in situ and was perfused by a modification of the Langendorff technique Adult mongrel cats weighing 2 to 4 kilograms were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg per kilogram of body weight) Animals were ventilated with room air by means of a tracheostomy cannula connected to a Harvard respirator The chest was opened by a midsternal incision The pericardium was excised. The perfusion catheter was introduced into the descending thoracic aorta and advanced so that its tip would lie just above the aortic valve The brachiocephalic and the left subclavian arteries were ligated close to their origin from the aortic arch The aorta was tied just below the arch The coronary arteries were then perfused with oxygenated Tyrode solution from a reservoir placed 70 cm above the level of the heart (perfusion pressure, 51 mm Hg) Through all stages of all experiments the perfusion pressure was kept constant The pulmonary artery was incised close to the right ventricular outflow tract to prevent distension of the right ventricle The heart was excised and transferred to a Lucite chamber

Complete atrioventricular block was produced by severing the Bundle of His. The free wall of the right ventricle was excised. A papillary muscle arising from the interventricular septum was selected and tied off at its apex with 5 0 silk Its attachment to the chordae tendinae was cut The muscle was then threaded through a metal ring mounted on a micromanipulator (Fig 1) The

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Table III Effect of acidic pH (6 97 to 7 05) on force compared to control pH (7 20 to 7 25) after five and ten minutes of perfusion

Time (minutes)	*Force (mean ± S.E.M.)*	*dF/dt (mean ± S.E.M.)*	*P*†
5	93 ± 11	104 ± 12	NS‡
10	90 ± 13	93 ± 14	NS

Expressed as per cent f control.
†P obabil ty
‡NS not signifi ant.

was then resumed at the same flow rate as in the control state to study the degree of recovery of force on re establishing normal perfusion After a minimum period of 10 minutes of perfusion with Tyrode solution or when a steady state of force development was reached the perfusate was changed to one containing 0 5 mM ATP The force was recorded until a new steady state was reached

(B) In the above set of experiments glucose was present in the perfusate through all stages of the experiments. To assure that exogenously ad ministered ATP was the only source of high energy phosphates, glucose was eliminated from the perfusate during the postischemic phase Twelve experiments were performed.

Group II (A) Observations were made on the effect of 0 5 mM ADP 0 5 mM AMP and 0 5 mM adenosine on the force developed by muscles in the postischemic state and their effect compared with that of 0 5 mM ATP

(B) Observations were made on the effect of 2 0 mM ADP 2 5 mM AMP and 2 5 mM adenosine on the force developed by muscles in the postischemic state and their effect compared with that of 0 5 mM ATP

Group III Observations were made on the effect of varying the concentration of ATP on the force developed by postischemic muscles. ATP was used in 0 01 0 1 0 5 1 0 and 2 5 mM concentra tions. Records were made for at least five minutes of perfusion at each concentration

Group IV Four experiments were performed to study the relationship between the effect of ATP perfusion on force development by postischemic muscles and duration of ATP perfusion i e to study if ATP produced a transient or a lasting change In the postischemic period, 0 5 mM ATP was perfused successively for 5 10 15 and 30

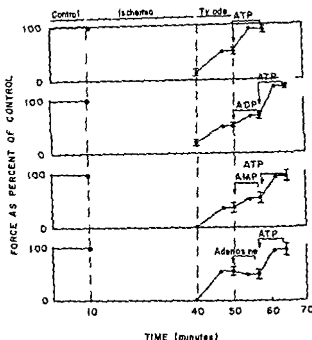


Fig 3. Effect of 0 5 mM ATP ADP AMP and adenosine on the contractile force of the papillary muscles in the postischemic state During ischemia force was measured only at the time of termination of the ischemic stage After a steady state of force development was reached during postischemic perfusion of ADP AMP and adenosine ATP was perfused to compare its effect with that of ADP AMP and adenosine The values are mean ± S.E.M of the corre sponding number of experiments (n) as shown in Table IV

minutes followed in each instance by an identical period of perfusion with Tyrode solution

Group V Observations were made on the effect of adenine nucleotides on force development by muscles in the control state All compounds were used in 0 5 mM concentration After recording the control force the perfusate was changed to one containing the substance being studied. Force was recorded until a new steady state was reached.

Results

As shown in Table I addition of adenine nucleotides lowered the pH of the perfusate to as low as 6 94 with 2 5 mM ATP To determine the effect of lowered extracellular pH alone on force development by the papillary muscles six experi ments were performed in which after obtaining control records, muscles were perfused with Tyrode solution (pH 6 97 to 7 05) for up to 10 minutes (change in force secondary to change in

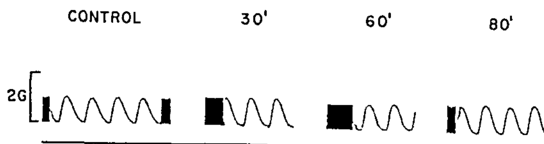


Fig 2. Representative record of force developed by isometrically contracting in situ feline right ventricular papil lary muscle Up to 80 minutes there is minimal variation in force The muscle diameter was 0 8 mm and the force was 2 0 grams per square millimeter

millimeter to 3 5 grams per square millimeter The maximum force developed by these muscles when perfused with a modified Tyrode solution containing 10 8 mM Ca^{++} and 103 mM Na^{+} varied from 4 0 to 8 0 grams per square millimeter The perfusion flow rate ranged from 10 to 30 ml per minute in this series of experiments but did not change significantly in any one experiment (ex cept secondary to the action of adenosine and adenosine 5 monophosphate, sodium salt) The preparation showed reasonable stability for up to 80 minutes under control conditions (Fig 2) with only minor changes in developed force In six hearts, the wet and dry weight of the right ventricular free wall excised at the beginning of perfusion and the wet and dry weight of the rest of the heart after four to five hours of perfusion were compared There was only minimal myocar dial edema as a result of four to five hours of per fusion (+1 4 per cent of the control wet weight) Ischemia* was produced by total cessation of per fusion In all experiments the ischemic period consisted of 30 minutes

Addition of adenine nucleotides† to Tyrode solution is expected to bind calcium thus lower ing the ionized calcium concentration in the per fusate which may affect the development of force by the muscles To determine the degree of calci

Table II Ionized calcium concentration in Tyrode solution before and after addition of various substances studied

	Ca^{++} concentration (mM/L)
Tyrode solution	1 8
0 5 mM adenosine	1 8
2 5 mM adenosine	1 7
0 5 mM AMP	1 7
2 5 mM AMP	1 7
0 5 mM ADP	1 7
2 0 mM ADP	1 25
0 5 mM ATP	1 38
2 5 mM ATP	0 68

um binding by the adenine nucleotides, the ionized calcium concentration in Tyrode solution was measured before and after the addition of various adenine nucleotides using the ion selec tive electrode technique (Orion Manufacturing Company, Cambridge, Mass) Our findings are shown in Table II

Tests of the significance of differences between mean values of various groups reported in this study were calculated by means of the standard Student s t test All mean values are followed by the standard error of the mean as the index of dispersion *The following groups of experiments* were performed.

Group I (A) Observations were made on the effect of 0 5 mM ATP on the contractile force of postischemic muscles After recording the con trol force, ischemia was produced by total cessa tion of perfusion for 30 minutes There was a severe decrease in force at the end of the ischemic period. Perfusion with Tyrode solution

The term ischemia is incorrect as used here since the perfusate in our studies was not blood. Ischemia indicates the lack of flow of blood, the nutrient fluid, and since in our experiments the flow of the perfu sion fluid was discontinued, we have used the term ischemia to emphasize lack of oxygen as well as lack of coronary flow

†Adenosine and AMP were obtained from Sigma Chemical Company St. Louis Mo and adenosine diphosphate disodium salt—ADP and adenosine triphosphate disodium salt—ATP were obtained from Mann Research Laboratories Division of Becton Dickinson & Co New York N Y

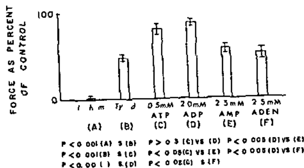


Fig 4. Effect of 0 5 mM ATP on the contractile force of the papillary muscles in the postischemic state compared with the effect of 2 0 mM ADP 2 5 mM AMP and 2 5 mM adenosine (ADEN) on the same muscles in the postischemic state Both 0 5 mM and 2 0 mM ADP caused a significant recovery of force of the muscles in the postischemic state while 2 5 mM AMP and 2 5 mM adenosine did not Bars represent mean ± S.E M of four experiments.

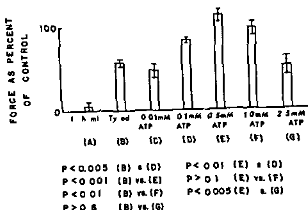


Fig 5 Effect of various concentrations of ATP on the force *developed* by papillary muscles in the postischemic state Bars indicate mean ± S E of four experiments The difference between the effect of 0 5 mM ATP and 1 0 mM ATP was not significant (P > 0 1)

Table VI Force the maximal rate of rise of tension (+dF/dt max.) and the maximal rate of fall of tension (−dF/dt max) during postischemic perfusion with Tyrode solution compared with that during postischemic ATP (0 5 mM) perfusion *Each variable is expressed as per cent of control**

Postischemic Tyrode (mean ± S E M)			*Postischemic ATP (mean ± S.E.M.)*		
Force	*+dF/dt max*	*−dF/dt max.*	*Force*	*+dF/dt max.*	*−dF/dt max.*
48 ± 11	63 ± 12	52 ± 11	106 ± 13	115 ± 11	127 ± 18

Th difference betw en Fo ce +dF/dt max. and −dF/dt max. during postischemic Tyrode pe fus on and during postischemic ATP perfus n was sig nificant, p < 0 01 p < 0 005 and p < 0 01 respectively

mine whether the effects of ATP on the postischemic heart were due to the intact molecule entering the cell or possibly due to a breakdown product entering the cell and being rephosphorylated intracellularly As described above adenosine AMP and ADP in 0 5 mM con centration did not significantly affect the force of postischemic muscles Fig 4 illustrates the effects of 0 5 mM ATP 2 0 mM ADP 2 5 mM AMP and 2 5 mM adenosine on the force developed by mus cles in the postischemic state Both 0 5 mM ATP and 2 0 mM ADP caused significant recovery ($P < 0$ 001 and $P < 0$ 001 respectively) while 2 5 mM AMP and 2 5 mM adenosine did not. The difference between the effect of 0 5 mM ATP or 2 0 mM ADP and that of 2 5 mM AMP and 2 5 mM adenosine was significant ($P < 0$ 05)

In six experiments the maximal rate of rise of tension (+dF/dt max) and the maximal rate of fall of tension (−dF/dt max) were measured (Ta ble VI) during the control state during the postischemic perfusion with Tyrode solution and during ATP perfusion ATP caused significant recovery in the rate of rise as well as in the rate of fall of tension ($P < 0$ 005 and $P < 0$ 01 respec tively) This observation indirectly suggests that exogenously administered ATP did reach the in tra cellular sites where ATP is utilized in both the contraction and the relaxation process

Concentration and time relationship of postischemic recovery by ATP ATP caused sig nificant recovery of force in the postischemic state in 0 1 0 5 and 1 0 mM concentrations (Fig 5) The difference between the effects of 0 1 mM ATP and 0 5 mM ATP was significant ($P < 0$ 01) That between 0 5 mM ATP and 1 0 mM ATP was

Table IV Effect of adenosine* and its nucleotides on the contractile force of postischemic papillary muscles

No of experiments		Force (per cent of control) (mean ± S.E.M.)		Significance
N = 16	Ischemia	13 ± 4	(A)	P < 0 001 (A) vs. (B)
(ATP)	Tyrode	49 ± 4	(B)	P < 0 001 (B) vs. (C)
	ATP	95 ± 7	(C)	P < 0 001 (A) vs (C)
n = 3	Ischemia	16 ± 3	(A)	P < 0 05 (A) vs (B)
(ADP)	Tyrode	46 ± 9	(B)	P > 0 05 (B) vs. (C)
	ADP	71 ± 6	(C)	P < 0 005 (B) vs (D)
	ATP	116 ± 3	(D)	P < 0 005 (C) vs. (D)
n = 5	Ischemia	1 ± 1	(A)	P < 0 02 (A) vs (B)
(AMP)	Tyrode	33 ± 10	(B)	P < 0 01 (B) vs. (D)
	AMP	49 ± 10	(C)	P > 0 25 (B) vs. (C)
	ATP	87 ± 9	(D)	P < 0 05 (C) vs. (D)
n = 5	Ischemia	2 ± 2	(A)	P < 0 05 (A) vs (B)
(Adenosine)	Tyrode	57 ± 11	(B)	P > 0 6 (B) vs. (C)
	Adenosine	50 ± 9	(C)	P > 0 05 (B) vs (D)
	ATP	97 ± 14	(D)	P < 0 025 (C) vs (D)

All compounds were used in 0 5 mM concentration.

Table V Effect of glucose free Tyrode solution and 0 5 mM ATP in glucose free Tyrode solution on contractile force of postischemic papillary muscles

No of experiments		Force (per cent of control) (mean ± S.E.M.)		Significance
	Ischemia	5 ± 1	(A)	P < 0 001 (A) vs (B)
12	Tyrode	39 ± 5	(B)	P < 0 001 (B) vs (C)
	ATP	77 ± 8	(C)	P < 0 001 (A) vs. (C)

perfusate occurred quite rapidly, usually in less than 5 minutes in our preparation) The pH was adjusted by altering the bicarbonate content of the Tyrode solution Results of these experiments (Table III) suggest that within the pH range of this investigation, force was not significantly altered by a low pH of the perfusate

Effect of adenine nucleotides on the force developed by muscles in the postischemic state Table IV and Fig 3 illustrate the effect of various compounds (in 0 5 mM concentration) on recovery of force after ischemia During the first 5 to 10 minutes of ischemia, force declined rapidly and then it declined gradually After 30 minutes of ischemia, force decreased to between 1 and 16 per cent of control in various groups of experiments Postischemic perfusion with Tyrode solution increased the force to between 33 and 57 per cent of control Although this recovery was statistically significant the peak force was still well below the control level Perfusion with 0 5 mM ATP further increased force and the difference between the force developed during postischemic perfusion with Tyrode solution and that during postischemic ATP perfusion was highly significant (P < 0 001) ADP, AMP, and adenosine (all in 0 5 mM concentration) did not significantly change the force developed by muscles in the postischemic state The difference between the force developed during ATP perfusion and that during perfusion of ADP, AMP, and adenosine was significant (P < 0 005, P < 0 05, and P < 0 025, respectively) ATP (0 5 mM) also caused significant recovery of force in the postischemic state when glucose was absent from the perfusate (Table V)

Transport of ATP from extracellular space A series of experiments was performed to deter

substance presumably calcium from the sarcoplasmic reticulum (3) binding of calcium to troponin to remove the inhibition on actin myosin interaction (thus generating force) and (4) active re uptake of calcium by sarcoplasmic reticulum (thus effecting relaxation) Of these processes the actin myosin interaction and re uptake of calcium by SR are known to require energy in the form of ATP[14] Depression of myocardial contractility after ischemia may be caused by depletion of ATP at any one or more of these sites. Studies by Kardesch Hogenkamp and Bing[15] and Trautwein and Dudel[16] have shown that ischemic myocardium shows little alteration in excitability while displaying marked changes in contractility Thus it would seem that depletion of ATP at any one or more of the intracellular sites involved in the contractile process may be responsible for the contractile failure The observation that ATP caused significant recovery of the rate of rise of tension and the rate of fall of tension suggests that exogenously administered ATP did reach the intracellular sites where it is utilized in the process of contraction and relaxation Thus a very close association between decreased high energy phosphates and decreased contractility in ischemic heart failure is established in our study

Since ATP was found to reverse the contractile failure of the postischemic muscles it is important to know whether ATP can enter the cell intact. The mechanism of transport of ATP cannot be clarified from these observations. However some inferences can be drawn Since the mean intracellular concentration of ATP in hypoxic failing myocardium is higher than 0 5 mM per liter[5,6,11,19] the perfused ATP (in 0 5 mM per liter concentration) either required active transport across the cell membrane or was dephosphorylated outside the cell and resynthesized inside the cell from its breakdown products as suggested by Hoffman and Okita[17] and Hattori Miyazaki and Nakamura[18] The perfused ATP may have provided energy for its own transport across the cell membrane and be degraded to ADP in the process The ADP thus formed is probably resynthesized to ATP in the cell. We also found that 0 5 mM ADP did not cause significant recovery of force of postischemic muscles while 2 0 mM ADP did. The mean intracellular concentration of ADP in hypoxic failing myocardium is reported to be higher than 0 5 mM per liter but lower than 2 0 mM per liter[5,6,19] This would suggest that in a 2 0 mM per liter concentration, ADP entered the cell by passive diffusion along a concentration gradient and was resynthesized to ATP in the cell to provide energy for contraction The exogenously administered ADP (or ADP from the exogenous ATP dephosphorylated outside the cell) may enter the cell and provide substrate for ATP synthesis as well as stimulate depressed oxidative phosphorylation in the mitochondria

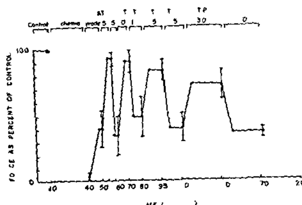


Fig 6 Effect of duration of ATP perfusion on the duration of recovery of postischemic contractile force The recovery was sustained only as long as ATP was perfused. Also the force diminished gradually as the duration of ATP perfusion increased.

The effects of adenine nucleotides on the contractility of normal myocardium have been found to be variable Brashear Mandelbaum and Ross[20] reported a positive inotropic effect of ADP on canine hearts studied with right heart bypass. Angelakos and Glassman[21] reported decreased myocardial tension with ADP in atropinized dogs Stepanenko and Bobrova[22] reported a triphasic action of ATP on fatigued frog heart a rapid rise in force immediately after the addition of ATP followed by a fall in force below the control level followed finally by a gradual rise in force Buckley Tsuboi and Zeig[23] reported that adenosine had a negative inotropic effect on the isolated perfused heart In our studies ATP ADP and adenosine caused a statistically insignificant decrease in force

Siska and co workers[24] reported that intracoronary administration of ATP had a protective effect on canine hearts subjected to ischemic

Table VII Effect of adenosine and its nucleotides on the contractile force of normal muscles*

No experiments	Compound	Force (per cent of control) Mean ± S.E.M.
4	ATP	57 ± 8†
4	ADP	72 ± 7†
5	AMP‡	104 ± 6†
5	Adenosine‡	78 ± 3†

*All compounds were used in 0.5 mM concentration
†Difference from control not significant, P > 0.05
‡Coronary flow rate increased by 40 to 50 per cent above control.

not significant (P > 0.1). The difference between the force during 2.5 mM ATP perfusion and that during postischemic perfusion with Tyrode solution was not significant (P > 0.6). This was possibly due to significant lowering of ionized calcium concentration (see Table II) in Tyrode solution by the calcium chelating effect of ATP.

Since ATP caused significant recovery of force in the postischemic state, it was of interest to find out if the effect of ATP was transient or lasting. Fig. 6 shows that the effect was transient, being present only as long as ATP was perfused. When the perfusate was changed to Tyrode solution following 5, 10, 15, and 30 minutes of ATP perfusion, force quickly returned to pre-ATP level.

Inotropic effects of adenine nucleotides on normal ventricular myocardium. ATP, ADP, and adenosine caused a slight but statistically insignificant decline in force of normal papillary muscles. AMP caused a slight but statistically insignificant increase in force (Table VII). AMP and adenosine increased the coronary flow rate by 40 to 50 per cent above control. The increase in flow was most likely due to reduction in coronary vascular resistance since the perfusion pressure remained unchanged.

Discussion

The most significant finding in this study was that ATP reversed the contractile failure of the muscles in the postischemic state. The manner in which ATP restored the contractile force of the postischemic muscles is not conclusive from our study. Greiner,[8] Furchgott and DeGubareff,[7] and Feinstein[6] have reported decreased myocardial contractility following hypoxia associated with decreased myocardial concentration of CP and ATP, the reduction in CP being much greater and much more rapid than the reduction in ATP. Feinstein[6] found that, although during asphyxia guinea pig hearts showed contractile failure and reduced concentration of CP and ATP, on re-establishing ventilation there was prompt recovery of contractile function of these hearts while CP and ATP levels remained quite low. We did not measure myocardial concentration of CP and ATP in our study. Although a cause and effect relationship between decreased high energy phosphates and decreased myocardial contractility in ischemic heart failure is not established in our study, the reversibility of contractile failure by ATP suggests such a relationship. Pool and co-workers[11] reported a moderate decrease in CP and no significant change in ATP levels in acutely induced hypoxia in dogs at the time of hypoxic heart failure. The period of hypoxia in their study was only 13 to 17 minutes and the level of hypoxia was not severe (arterial O_2 saturation 40.9 ± 6.8 per cent). It is possible that in their study and in Feinstein's study, the level of ATP had not decreased because it was resynthesized from CP. The CP level was definitely lowered in both studies.

Weissler and co-workers[12] and Burdette and co-workers[13] have described mitochondrial damage following hypoxia or anoxia which may be responsible for decreased energy production. It is possible that perfused ATP may have been utilized in mitochondrial repair but this is at best incomplete since in our study the recovery caused by ATP (Group IV) was only transient despite up to 30 minutes of perfusion with ATP. The recovery was sustained as long as exogenous ATP was supplied which suggests that in acute ischemic heart failure, energy production is impaired even though energy utilization may remain normal. Oxygenated Tyrode solution containing glucose did not restore the force in the postischemic period while ATP reversed the contractile failure even in the absence of glucose, the only substrate for energy production present in the perfusate. This finding is in accord with biochemical studies which suggest that oxidative phosphorylation, and hence energy production, is impaired in acute ischemic heart failure.[5,6]

Myocardial activation and relaxation in most vertebrates involves several interrelated processes. These are (1) generation and propagation of action potential, (2) release of an activating

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asystole and subsequently resuscitated They found lower lactate and inorganic phosphate levels and higher glycogen, CP, and adenine nucleotide levels in ischemic hearts given ATP as compared to those not given ATP, indicating reduced or no anaerobic glycolysis for energy production in these hearts Clinical use of ATP in acute ischemic heart failure in man is not possible since human serum contains ATPase[25] which will degrade ATP to ADP and inorganic phosphate ADP so produced can cause platelet aggregation and disseminated intravascular thrombosis before the high energy phosphate can reach the myocardium

Summary

Effects of adenine nucleotides on contractile force of normal and postischemic ventricular muscle were studied Experiments were performed at room temperature on Langendorff perfused feline right ventricular papillary muscle preparation remaining in situ Peak systolic force developed by normal muscles was not significantly altered by adenine nucleotides in the concentrations used Complete cessation of coronary perfusion (ischemia) for 30 minutes caused severe contractile failure which was not completely reversed on resumption of perfusion with oxygenated Tyrode solution ATP (0 5 mM) and ADP (2 0 mM) caused significant recovery of force of failing postischemic muscles while 0 5 mM ADP, 0 5 mM AMP 2 5 mM AMP 0 5 mM adenosine, and 2 5 mM adenosine did not These findings show that the contractile failure of ventricular muscle subjected to acute ischemia can be reversed by administration of high energy phosphates The recovery however is not sustained after nucleotide perfusion is stopped There is suggestive evidence that ATP does not enter the cell intact but may enter the cell in the form of ADP

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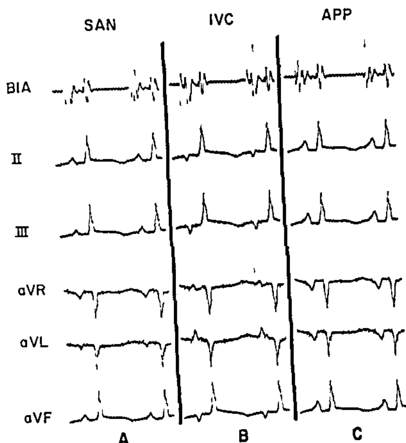


Fig 1 Right atrial (RA) stimulation. The P wave is upright during stimulation of the sino atrial region (SAN) in *A*, and of the right atrial appendage (APP) in *C* and becomes inverted during stimulation of the inferior aspect of the RA near the inferior vena cava (IVC) in *B* Time lines = 0 1 sec and 0 01 sec in Figs 1 3 and 4 BIA. Bipolar intra cavitary electrogram

and electrocardiograms were displayed on a commercially available eight channel oscilloscope and recorded at a paper speed of 100 mm per second on a commercially available multichannel oscillographic recorder equipped with light galvanometers with a linear frequency response from zero to 8 000 Hz. Time lines of 100 and 10 msec. were inscribed on the photographic paper by an independent time line generator

Results

Normal sinus rhythm (NSR) NSR was present in 13 of 14 animals and was manifested by positive P waves in Leads II III and aV_F and negative or biphasic P waves in Leads in aV_R and aV_L The P wave was biphasic and of low amplitude in Lead I in 5 of 14 animals and positive but of low amplitude in the other 9 animals. It was usually biphasic in Lead V_1 and positive in all the other precordial leads (V_2 V_6) In one animal (M4) the P wave was negative in Leads I and V_6 and positive in Leads II and III suggesting that the spontaneous rhythm did not originate in the S A node but elsewhere in the atria

Right atrial (RA) stimulation Stimulation of the inferior portion of the RA near the anterior aspect of the inferior vena cava (IVC) resulted in negative P waves in Leads II III and aV_F (Fig 1 Fig 2 *A* tracing 6) in 82 per cent (12 of 14) of the animals The P wave became positive in Leads aV_R and aV_L The polarity remained unchanged in Lead V_6 Stimulation of any other site on the anterolateral surface of the RA did not result in frank inversion of the P wave (Fig 1 *A* and *C*) but the contour of the P wave was usually altered, with frequent occurrence of a bifid P wave in Leads II III and aV_F. Transitional P waves with one negative and one positive compo

Ectopic atrial rhythms in the primate

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Controversy persists about the significance of the spatial orientation of the P wave and its relation ship to the site of origin of the atrial impulse[1] Whereas the diagnosis of A V junctional or of 'coronary sinus rhythm is usually made when the P wave is superiorly oriented (negative p in Leads II, III, and aV_F) experimental evidence has been accumulating which suggests that P wave polarity and spatial orientation are not always an infallible indicator of the site of origin of the P wave[1 9]

Most of the studies heretofore reported have consisted of electrocardiographic or vectorcar diographic observations carried out during electrical stimulation of the atria of canine or human hearts.

This communication reports the results ob tained during the experimental production of ec topic atrial rhythm in a different species of animals Rhesus monkeys and baboons at the time of thoracotomy and using a stimulating electrode with a small inter electrode distance

Methods

Ten Rhesus monkeys (*Macaca mulatta*) weigh ing 4 to 10 kilograms and 4 baboons weighing 9 kilograms were anesthetized with sodium pen tobarbital (3 to 5 mg per kilogram in travenously) A transverse thoracotomy was per formed in the fourth intercostal space and the heart was exposed and kept in its natural posi tion by a pericardial cradle The animal was first positioned in the left lateral decubitus position and stimulation of the right atrium at selected sites was performed under direct visualization, care being taken not to produce any significant change in the position of the heart with respect to the chest and great vessels For detailed stimulation of the left atrium, the animal was ro tated to the right lateral decubitus position, care again being taken not to produce any significant distortion in the normal anatomic position of the heart. In order to stimulate the posterior aspect of the left atrium, the apex of the left ventricle was lifted up gently and minimally out of its nor mal position in the pericardial cradle by means of an apical suture and the stimulating electrode was inserted toward the base of the heart and positioned just above the mitral annulus

Stimulation was performed with a hand held bipolar electrode consisting of two stainless steel elctrodes 0 5 mm in diameter situated 1 mm from each other and embedded in the concave side of a plastic head fashioned in the form of a shallow spatula The handle was made of a thin, hollow rigid tube in which two insulated stainless steel wires were connected to the electrodes and to the terminals of a constant current stimula tor The atria were stimulated at a regular rate slightly above that of the normal sinus rhythm and with stimuli which were just above threshold[1] Simultaneous electrocardiographic leads (limb leads and precordial Lead V_6 were recorded during normal sinus rhythm (NSR) and during atrial stimulation An electrogram was recorded with an electrode catheter positioned in the cavity of the right atrium The electrogram

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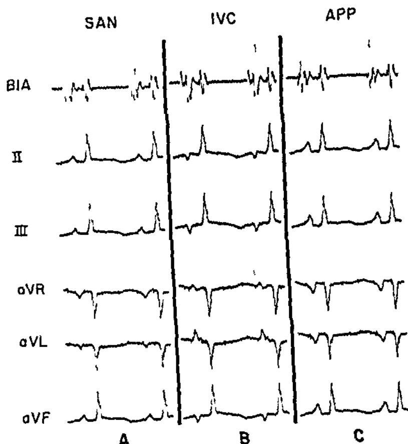


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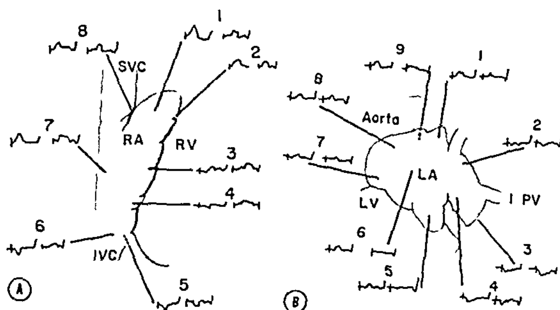


Fig 2. Representative P waves during stimulation of RA (in *A*) and LA (in *B*) The first and second P waves of each numbered *set represents Leads II* and V_6 respectively Set No. 1 represents stimulation of the sino atrial region

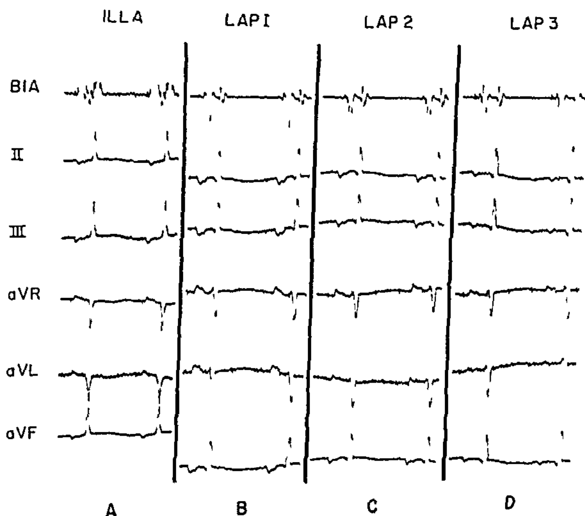


Fig 3 Inversion of P wave during stimulation of the infero-lateral left atrium (ILLA) near the left inferior pulmonary vein obtained in 10 out of 13 (77 per cent) animals, and *during stimulation* of three sites just above the mitral annulus on the posterior aspect of the LA (LAP 1 2 and 3)

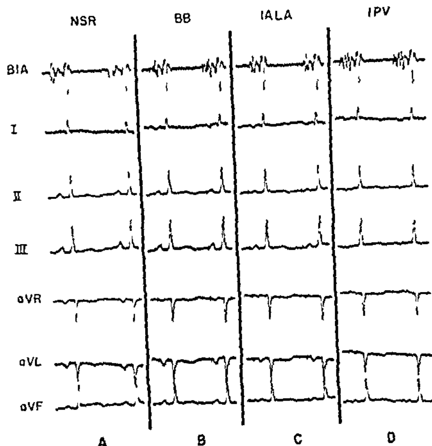


Fig 4 Alteration of P wave during NSR and during stimulation of the region of the Bundle of Bachmann (BB) the inferoanterior aspect of the LA (IALA) and the LA near the inferior pulmonary vein (IPV)

nent (– +) in Leads II III and aV_F could be detected during stimulation of the anterolateral aspect of the right atrium close to the tricuspid ring and IVC (Fig 2 *A* tracing 4)

Left atrial (LA) stimulation Stimulation of the atrial region posterior to the inferior vena cava resulted in inversion of the P wave in Leads II III and aV_F as well as in Lead V_6 This region is more properly considered left atrium than right atrium.[1]

Stimulation of the posterior aspect of the LA just above the mitral annulus resulted in negative P waves in Leads II III and aV_F (Fig 3 *B* through *D*) Stimulation of sites on the inferior epicardial surface of the LA near the left pulmonary veins also resulted in a negative P wave in Leads II III and aV_F in 10 of 13 animals (77 per cent) (Fig 2 *B* tracings 3 and 4 Fig 3 *A*) In 3 of 13 animals (23 per cent) the P wave was not frankly negative in Leads II III and aV_F instead there were two or three wavelets (+ – or –,+ or + – +) with broadening of the P wave A negative P wave in Lead V_6 was also seen in 5 of 8 (62 5 per cent) of the animals in which this was studied (Fig 2 *B* tracings 3 and 4) Transitional forms of P waves could also be detected in some animals when stimuli were applied between the two left pulmonary veins (Fig 2 *B*, tracing 2) Stimulation of other sites on the anterior surface consistently altered the contour of the P wave (Fig 4, *B* and *C*) and occasionally (Fig 4 *D*) the P wave became almost isoelectric or broken up into two (+ – or – +) or three small wavelets (+ – or – + or – + –) However the polarity of the P wave did not become frankly negative on stimulation of these sites.

P R interval The P R interval was not altered in a consistent direction or magnitude by pacing the various sites. While the P R interval tended to be longer during electrical pacing than during

NSR, it was also often shorter The P R interval was never excessively short, however The shortening could not be related to the lower location of the atrial pacing site with respect to the A V junction

Discussion

Normal sinus rhythm The P wave of the small primate (baboons and Rhesus monkeys) in NSR is similar to that of the dog and human with some minor differences [10,12] P waves are normally positive and tall in Leads II III and aV$_F$ whereas they are often isoelectric or biphasic and of low amplitude in Lead I The relatively high amplitude of the P wave in Leads II, III, and aV$_F$ makes the small primate a highly suitable experimental animal for the study of ectopic atrial rhythms, since vertical shifts in mean frontal axis are easy to detect. On the other hand, the low amplitude of the P wave in Lead I is such that changes in the direction of depolarization in the horizontal plane are difficult to detect. Thoracotomy imposes a further limitation on the interpretation of changes in Lead I by further decreasing the amplitude of the P wave in this lead Therefore changes of P wave polarity in Lead I cannot be fully described with complete confidence although several examples of negative P waves in Lead I were observed (Fig 4 *B* through *D*) P waves are usually positive in the left lateral precordial leads [10,11] as was found in this study

P wave polarity The present study demonstrates, for the subhuman primate that stimulation of certain regions of the right and left atria can often lead to negative P waves in Leads II III, and aV$_F$ Two of these areas (Fig 2, *A*, tracings 5 and 6, Fig 3, *B* through *D*) correspond to the caudal RA and the PLA region (postero inferior LA) described by Waldo and co workers[5] for the dog and human [1] In addition in monkeys and baboons stimulation of one other area the inferolateral region of the LA (Fig 2 *B* tracings 3 and 4, Fig 3, *A*) near the left inferior pulmonary vein can also lead to superiorly oriented P waves It is not clear from reported studies whether stimulation of this same area in man or in the dog does or does not lead to similar negative P waves and it would be of interest to further elucidate this point

The electrocardiographic diagnosis of upper A V nodal rhythms is based on negative P waves in Leads II, III, and aV$_F$ and a short P R interval [13,14] A diagnosis of "coronary sinus rhythm is made when P waves are similarly oriented and the P R interval is normal or lengthened [14] Experimental stimulation of the coronary sinus region has indeed been shown to result in negative P waves in Leads II, III, and aV$_F$ by Leon and co workers[15] and others [1,6,15]

However, as previously suggested,[1,19] the term coronary sinus rhythm' has become too restrictive at our present stage of knowledge for the following reasons First, in previous studies[1,6,15] as well as in the present study, stimulation of sites elsewhere in the lower part of the right atrium separate from the ostium of the coronary sinus also results in similar inversion of the P wave in Leads II, III, and aV$_F$ Second, as shown in the present study, and also previously by Waldo and co workers[1,5] stimulation of the posterior left atrium also results in reversal of P wave polarity in Leads II III, and aV$_F$. Aruguments have been advanced to support the hypotheses that certain atrial rhythms which, in man, show a superior mean P wave axis originate in that portion of the left atrium [9,17] Third, the present study shows that negative P waves in Leads II III, and aV$_F$ also occur upon stimulation of the inferolateral aspect of the left atrium near the left inferior pulmonary vein Fourth as shown by Wit and co workers,[18] a structure previously unsuspected as a site of pacemaker activity, the septal leaf of the canine mitral valve, contains cardiac cells which can act as pacemaker cells thereby suggesting another site which can probably produce arrhythmias Finally the presence of an A V junctional rhythm with retrograde capture of the atria and markedly delayed conduction to the ventricles can also result in a normal or prolonged P R interval and inversion of the P waves in Leads II III and aV$_F$ [14,15]

For these reasons, the designation of coronary sinus rhythm" should be avoided, the term low atrial rhythms' is a more appropriate term for rhythms characterized by inverted P waves in Leads II, III and aV$_F$ as previously suggested [1,19]

Attempts have been made by Leon and co workers[15] to use the precordial leads of the electrocardiogram in order to determine more precisely the site of origin of a superiorly oriented P wave Their results indicated a difference in the spatial orientation of the P waves obtained by stimulating the anterior margin of the IVC as op

7 No 6

posed to the more posteriorly located A V junction or coronary sinus However these results obtained as they were from normal young volunteer subjects, may not be applicable to older patients with atrial pathology Furthermore the apparent P wave vector obtained from inspection of the 12 lead electrocardiogram does not necessarily correspond accurately to the P wave loop obtained by vectorcardiography [7,20] The differentiation between A V junctional coronary sinus and lower atrial origin is therefore at best uncertain

The mechanism by which a superiorly oriented P wave results from stimulation of inferiorly located atrial regions has been investigated by previous authors.[1 6] The inferior location of these areas is not, in and by itself necessarily responsible for the appearance of a superiorly oriented P vector since stimulation of other inferior regions of the left and right atrium, for example near the A V valves anteriorly usually results in changes in configuration (flattening broadening or fragmentation) but not in frank reversal of polarity of the P waves (Fig 2 A tracings 3 and 4 Fig 2 B tracing 5) Waldo and co workers[1] postulated that inversion of the P wave in Leads II, III and aV_F is usually associated with early activation of the posterior aspect of the LA Excitation of this area is then followed by true radial spread and truly retrograde activation of the atria It would then have to be assumed that any ectopic rhythm whether it originates in the A V junction the coronary sinus or any other region of the right or left atria and which results in superiorly oriented P waves, does so because it spreads rapidly both to the inferior RA and to the postero inferior LA with subsequent retrograde radial activation of both atria This sequence of depolarization can reasonably be expected to occur with an impulse originating from the infero lateral LA (near the inferior pulmonary vein) as well as from the inferior RA As postulated by Waldo and co workers[1] such impulses would not succeed in spreading sufficiently rapidly to Bachmann s bundle and in depolarizing the contralateral atrium in a normal antegrade direction

The present study supports the contention of Mirowski that certain rhythms with negative P waves in Leads II III and aV_F may actually originate in the left atrium,[9] and that these rhythms may give rise to negative P waves in Leads I and V_6 as well (Fig 2 A, tracing 5 Fig 2 B, tracings 2 through 4 and Fig 4 B through D) The spontaneous occurrence of such rhythms has strong indirect support (for example, spontaneous diastolic depolarization occurs in cells of the left atrium) However the actual observation of spontaneously occurring LA rhythm in the animal in vivo must be considered at the present time not yet proved The conclusions of Mirowski that such rhythms can often be observed in the dog are based on the detection of early electrical activity in the posterior aspect of the LA [21] However it must be emphasized that the site of primary negativity was not identified and that simultaneous electrograms were not obtained from the inferior RA A rhythm originating in the latter region (truly a lower RA rhythm) would rapidly spread to the posteroinferior LA and would thus masquerade as LA rhythm [1]

Summary

P wave polarity was studied in small primates during electrical stimulation of both atria Negative P waves in Leads II III and aV_F were obtained during stimulation of the lower right atrium near the inferior vena cava the lower anterior left atrium near the inferior pulmonary vein and the infero posterior left atrium The P R interval was affected inconsistently These studies confirm findings originally observed in the canine and human heart, and call for caution in making the diagnosis of coronary rhythm and left atrial rhythm The term ectopic atrial rhythm seems preferable

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Experimental response curves A means of predicting pacemaker response to electrical interference

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Those cardiac pacemakers with a circuit designed to monitor ventricular depolarizations have been shown to be sensitive to a variety of electrical apparatus operating outside of the body and in the high frequency (3 to 30 MHz.) band of electromagnetic radiation [1 7] A series of experiments have been conducted which elaborate the significant aspects of electric field parameters which alter pacemaker function With this information a basis is laid for predicting in vivo pacemaker behavior to such interference

In this study three discrete frequencies (10 5 19 3 and 26 6 MHz.) were used to conduct two series of tests on demand type pacemakers The first series was a bench test Those units judged most sensitive during the bench tests were chosen for surgical implantation in large canidae At the time of the implantation a complete atrioventricular block was induced. Following a recovery period, the animals were subjected to the same test conditions as were used in the series of bench tests

Methods

The test facility[8] was a rectangular coaxial exposure transmission line The field strength E in volts per meter (v /M) within the exposure device can be calculated by measuring the average input power in watts P and using the relationship

$$E = 1/S\,(P\ Z/dc)^{1/2}$$

where S is the distance between the center and the outer conductor (0 714 meter) Z is the characteristic impedance of the line (50 ohms) and dc is the duty cycle The average power density P_d in milliwatts per square centimeter (mW/cm^2) can then be calculated by $P_d = (E^2/n)\,dc$ where n is the free space impedance of 377 ohms The electric field was also monitored with four fixed monopole probes mounted along the centerline of the exposure device The output of the probes was recorded on a strip chart recorder This reading is directly proportional to the field strength

$$E = K_b E$$

where E is the output of an electrometer and K_b is the slope factor (approximately 225 volts per meter)[9] These two methods of determining the electric field strength were found to agree within 10 per cent

For the bench tests the pacemakers were fitted with epicardial electrodes and placed on a lucite pedestal so that the pacemaker electrode system was perpendicular to the electric field vector A telemetry system was attached across the electrodes The telemetered signal was recorded as well as the field strength information

Those pacemakers with greatest sensitivity on the bench were resterilized and surgically implanted in canidae At the time of the implanta

The rese r h reported this paper was conducted by personn l of the Radiology D visio United States Air Forc School of Aerospace M d ici Aerospac Medical D ision, AFC, United States Air Force, Brooks Air Force Base T xas.

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The a mals i volved n this study were maintained and used in ac dance with the An mal W lfare Act of 19 0 and the "Guide f r the Care and Use of Laboratory Animals prepared by the National Academy of Sciences N tion l Research Council.

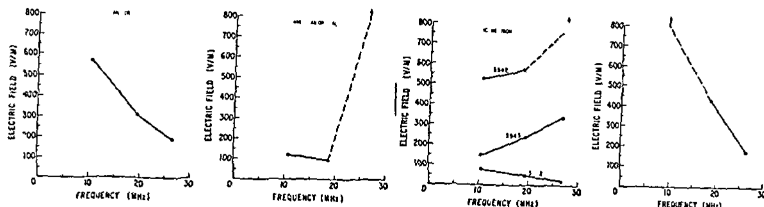


Fig 1 A through D Electric field (average E_t) versus frequency Data is from Cordis Stanicor American Optical Medtronic Models 5842 5942 5943 and General Electric units Three discrete frequencies were used for the electromagnetic tests (dark circles) with an interpolation between points being made The broken lines indicate that no E_t value was found for the frequency up to the limit of the exposure 800 v /m

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Exposures were made to each of the three discrete frequencies (10 5 19 3, and 26 6 MHz) using a pulse width of 1 5 milliseconds. A series of pulse repetition rates (100, 80, 60 40 30, and 20 pulses per second) were used with each of these three frequencies An exposure consisted of increasing the strength of the electric field to a maxium of 800 volts per meter while the frequency, pulse width, and pulse repetition rate were held constant The pulse repetition rate was changed and the procedure repeated until the series of repetition rates was completed

When complete inhibition cutoff was seen a rapid increase in the field strength was made to ascertain if the unit would operate at some higher level then the transmitter power was reduced. In all cases the pacemakers resumed normal function after the power was decreased Pacemaker function was never deprived for any period greater than 20 seconds The animals were repeatedly exposed to high frequency interference periodically over a six month period. Electrocardiographic tracings were taken weekly with no evidence of pacemaker failure following exposures to this electromagnetic radiation

Results

The point at which the pacemaker showed any change in rate was called the threshold level for that unit, E_t Quantification of the results in terms of the average power density required to attain a threshold level did not reveal consistency Using the relationship $P_d = KP_{av}$ where K is a constant,

$$K = \frac{Z}{(s)(n)}$$

indicated that the interference level was not directly proportional to the average power Calculation of the E field at the threshold level showed a repeated pattern of pacemaker response when several units from the same manufacturer and model were tested On this basis, the E field was determined to be the predominant factor

The significant parameters affecting pacemaker functions were found to be the magnitude of the electric field the pulse rate and the frequency (Table I) The threshold levels E_t have been plotted vs frequency allowing an estimate of E_t values over the high frequency band (Fig 1 *A* through *D*) For field strengths greater than E_t a relationship of the pacemaker rate vs the field

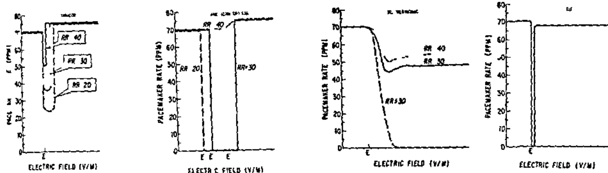


Fig. 2 A through D Response curves from in vivo artificial cardiac pacemakers derived by plotting pacemaker rate versus electric field threshold (average E_t)

Table I Average threshold levels by frequency for in vitro and in vivo pacemaker tests E_t values are the average taken from multiple exposures

	Bench test electric field (v/m)			*In vivo electric field (v/m)*			*Attenuation ratio*		
	Frequency (MHz)								
Models tested	*10.5*	*19.3*	*26.6*	*10.5*	*19.3*	*26.6*	*10.5*	*19.3*	*26.6*
Medtronic 5842	35	29	20	80	50	20	2.29	1.72	1
Medtronic 5942	512			530	570		1.04	<0.71	
Medtronic 5943	425	325	500	150	240	350	0.35	0.74	0.70
Cordis Stanicor	560	310	200	570	310	200	1.02	1	1
American Optical Monopolar	230	130	800	115	100		0.5	0.77	>1
General Electric A20720		400	200*		540	180		1.35	0.9

*No threshold value was obtained within the limits of the tests

strength for a particular pulse repetition rate yields an experimental response curve (Fig 2 *A* through *D*) The value of E_t was found to shift along the abscissa of the response curve However the response curves proved to be unique for a pacemaker of the same model and manufacturer This variation among similar units in E_t was on the order of 100 volts per meter Thus, an E_t value estimate can be obtained from Fig 1 for the pacemakers represented in these tests and applied to the appropriate response curve in Fig 2 to obtain a prediction of pacemaker rate for values greater than E_t

Discussion

As illustrated with the response curves, some pacemakers exhibited a window or a transition period. The transition period is defined as the E field width between two stable pacemaker rates. This transition period starts at the threshold level Above and below the window the pacemaker functioned at some rate although it may have been altered from its normal rate While in the window the pacemaker is completely inhibited.

The window range from Fig 2 *A* was determined to be between 100 v/M. (RR = 40) and 20 v/M. (RR = 20) The pattern indicated in this figure shows that a complete cutoff might be obtained at lower pulse rates. In Fig 2 *B* the pacemaker rate is strongly dependent on the pulse rate The interference observed at pulse rates greater than 40 p p m was an increase in the pulse rate of the pacemaker Complete cutoff occurred at the lowest pulse rate 20 p p s At a pulse rate of 30 p p m, the window was 150 v/M Similarly Fig 2 *C* shows a transient period of 60 v/M width In a slightly different manner Fig 2 *D* misses only a few pulses during the transition period. The rate to the response curve after E_t (other than a very narrow level for inhibition) is the fixed rate for the given pacemaker model

When the results of the bench and in vivo test

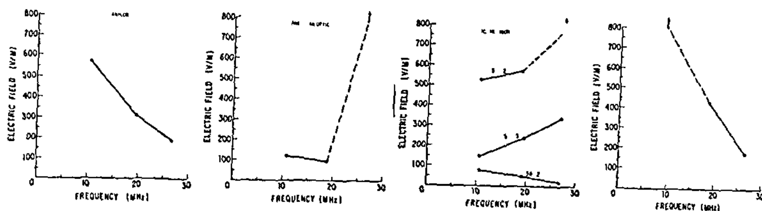


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Effects of diphenylhydantoin on coronary resistance and myocardial contractile force before and after ouabain

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Jerry B Scott Ph D *
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Diphenylhydantoin (DPH) sometimes terminates cardiac arrhythmias arising spontaneously or induced by digitalis [1,2] The mechanism(s) responsible for this antiarrhythmic action, however is not clear [1,3] In experimental animals DPH reportedly reduces coronary resistance [4-7] Thus it has been suggested that part of the antiarrhythmic effect of DPH may be related to enhanced coronary blood flow [4-6] Whether DPH actually elevates coronary flow in patients with coronary artery disease is questionable[1] and there appears to be no data on the response of the coronary vasculature to DPH after digitalis even in experimental animals We have recently shown that the vasoactivity of the potassium ion is greatly altered by ouabain [8] It is possible that the vasoactivity of DPH,[9,10] like potassium may be related to its effect on the activity of the digitalis sensitive Na^+ K^+ ATPase located on the membrane of the vascular smooth muscle cell If true digitalis should also alter the vascular response to DPH. The purpose of the present study was to examine this possibility in the intact dog heart

Methods

Mongrel dogs ranging in weight from 15 to 25 kilograms were anesthetized with sodium pentobarbital (33 mg per kilogram of body weight) and placed on positive pressure ventilation After intravenous injection of sodium heparin (5 mg per kilogram of body weight) the heart was exposed by opening the chest between the fourth and fifth ribs An extracorporeal circuit containing a constant output blood pump was interposed between the left femoral artery and the left common coronary artery The method used to cannulate the coronary artery has been previously described in detail [11] Initially coronary flow was set at a level that produced a mean perfusion pressure of approximately 120 mm Hg and flow was then maintained constant throughout the experiment Left ventricular contractile force was measured by attaching a strain gauge arch to the surface of the left ventricle Aortic pressure coronary perfusion pressure and contractile force were continuously recorded on a direct writing oscillograph

After suitable control measurements were obtained, diphenylhydantion sodium (50 mg per milliliter) was infused at sequentially higher rates into the coronary perfusion circuit (proximal to the blood pump) The infusion rates used were 0 01 0 021 0 05 and 0 10 ml per minute Each rate of infusion was maintained until the measured hemodynamic parameters were in a steady state (usually 2 to 3 minutes)

Following recovery from drug infusion an intracoronary infusion of ouabain (12 μg per minute) was begun After 17 minutes the ouabain infusion was terminated and the response to DPH re evaluated A previous study[12] from this laboratory demonstrated that intracoronary administration of this dose of ouabain either blocked or reversed the coronary vascular response to hypokalemia In order to determine if the coronary response to moderate hyperkalemia is also altered by ouabain in each of the present

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were compared, the difference in the nature of the response was only in the value of E_t. A direct comparison of the E_t values from each of these series was made by calculating an attenuation ratio, AR, (Table I). The AR is the quotient of the threshold level determined from the in vivo testing divided by the threshold levels determined from the bench testing. Values less than one were not expected since the electric field should follow a decaying exponential across the skin.[10] Thus the E field at the implanted pacemaker site is only a fraction of the field outside the skin. The consistent findings over a period of six months excluded any explanation based on early postsurgical changes. The periodic monitoring of the pacemakers revealed no malfunctions. For the AR to be less than one raises questions as to how the coupling between the electric field can be greater in vivo than in vitro. Possible explanations arise when those parameters which differed between the two series of tests are examined: (1) the electrode configuration within the body of the animals consisted of loops and coils so that the orientation of the electrodes with respect to the electric and magnetic fields could not be controlled; (2) the size of the animal when compared to the distance between the center and outer conductor is significant and may cause an unrecorded electric field perturbation in the animal not present in the bench tests.

In applying these results to pacemaker patients, we consider our test conditions to represent the worst case situation. The test animal was carefully oriented and stationary to an electrical interference which was very uniform. An individual would have to encounter a very uniform field and remain stationary in order to duplicate our test situation. A closer approximation to the test condition would exist in the clinical or surgical situation with the use of diathermy or cautery where the patient is stationary and the electric field is in proximity to the patient. The E_t estimates which we have reported and the response curves would provide a reasonable level of safety in the latter situation and an additional margin of safety in the case of the ambulating patient in a nonuniform field.

Summary

In vivo testing of noncompetitive pacemakers has produced quantification of the threshold levels of electrical field strength in the high frequency range (3 to 30 MHz.) which will alter pacemaker function. Response curves have been constructed to show the qualitative behavior of these pacemakers to electrical fields greater than threshold values. An attenuation ratio between the implanted and the free field threshold level has been determined for each pacemaker tested.

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In contrast hyperkalemia reduced myocardial contractile force before and after ouabain

Discussion

These studies show that in the *in situ* canine heart perfused at constant flow (1) intracoronary administration of DPH produces a fall in coronary vascular resistance and myocardial contractile force and these effects are not altered by ouabain (2) ouabain itself acts directly to increase coronary resistance and myocardial contractile force (3) the vascular but not the myocardial response to moderate local hyperkalemia is changed by ouabain

Previous studies[4-6] have shown that coronary vascular resistance is reduced following systemic injections of DPH in the undigitalized animal however only one study indicates that the fall in resistance is due to a direct effect of DPH on the coronary vasculature[7] In the present study intracoronary infusion of DPH reduced coronary resistance before there was a demonstrable change in systemic pressure thus ruling out reflex mediation of the response Infusion of the solvent at the same rates as DPH failed to affect coronary resistance indicating (1) that DPH was the active principle and (2) that the reduction in coronary resistance produced by DPH was due to an increase in blood vessel diameter rather than a dilutional decrease in blood viscosity The increase in blood vessel diameter probably resulted from (1) a direct effect of DPH to relax vascular smooth muscle and (2) a passive expansion of coronary vessels produced by an increased transmural pressure mediated through a fall in extravascular pressure The fall in myocardial contractile force suggests the latter mechanism while the magnitude of the fall in coronary resistance suggests the former mechanism

The rise in coronary resistance produced by ouabain and the failure of ouabain to influence the coronary or myocardial response to DPH is of interest because it could shed some light on the mechanism of action of this compound. We have previously reported that intra arterial infusion of ouabain into the canine forelimb or gracilis muscle elevates vascular resistance[8] The same is true for the vascular beds supplied by the superior mesenteric and common carotid arteries.[13] Bloor and colleagues[14] recently reported that an intracoronary bolus injection of ouabain elevated coronary resistance in two unanesthetized dogs. Thus, it is difficult to escape the conclusion that ouabain acts directly to constrict blood vessels In a previous communication[8] we proposed a cellular mechanism to account for this constriction Briefly we hypothesized that ouabain inhibits the vascular cell membrane Na^+ K^+ ATPase (electrogenic sodium-potassium pump) which in turn causes the intracellular accumulation of positive charges depolarization and constriction In the same communication we suggested that the vasodilator action of potassium is related to stimulation of the vascular cell membrane Na^+ K^+ ATPase activity resulting in hyperpolarization and relaxation Consequently after inhibition of the sodium potassium pump by ouabain the vascular response to potassium should be blocked or reversed. Indeed this was the case in the previous study of the forelimb and gracilis muscle[8] and in the present study of the coronary bed. DPH is reported to stimulate Na^+, K^+ ATPase activity in brain tissue[9,10] but not in cardiac tissue[3,15] The effect of DPH on sarcolemmic Na^+ K^+ ATPase activity in vascular smooth muscle is unknown If DPH does increase the activity of the vascular cell membrane Na^+ K^+ ATPase then part or all of its vasodilator properties might be related to this action The present study detracts from this possibility however since the coronary vasodilator effect of DPH was not altered in a preparation in which the sodium potassium pump was inhibited, as evidenced by the fact that the response to moderate hyperkalemia was suppressed or reversed. Neither can beta receptor stimulation be invoked to explain the vasodilator action of DPH since it is not altered by propranolol.[7] Finally, it is difficult to explain the dilation on the basis of an increase in metabolite concentration or a fall in tissue oxygen tension In the present study myocardial metabolism fell (presumed from the fall in contractile force) while coronary blood flow remained constant. Under this condition one would predict a fall in myocardial metabolite concentration and a rise in myocardial tissue oxygen tension Also following intravenous injection of DPH coronary resistance is reduced while coronary sinus flow and oxygen tension are elevated.[5,6]

Numerous investigators, employing a variety of techniques, have shown that DPH produces some degree of myocardial depression before digitalis[3,4,16-18] The present observations coupled

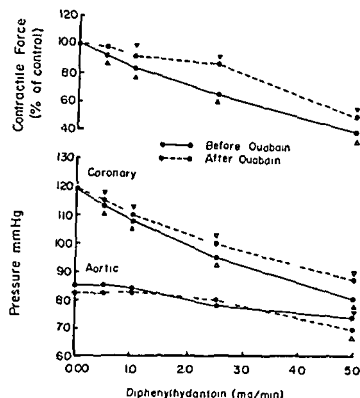


Fig 1 Average effects (N = 8) of an intracoronary infusion of DPH on myocardial contractile force coronary perfusion pressure and aortic pressure before and after ouabain Coronary blood flow = 137 ml/min Δ denotes a significant change at p < 0 05 level relative to the control

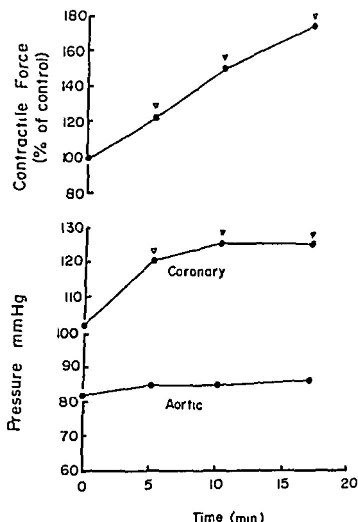


Fig 2 Average effects (N = 8) of an intracoronary infusion of ouabain (12 μg/min for 17 minutes) on myocardial contractile force coronary perfusion pressure and aortic pressure during constant flow (137 ml/min) perfusion of the left common coronary artery Δ denotes a significant change at p < 0 05 level relative to the control

experiments an isotonic solution of potassium chloride was infused directly into the coronary perfusion circuit before and after ouabain The infusion rate was calculated to elevate the potassium concentration in the inflowing coronary blood by approximately 2 5 mEq /L The sequence of the potassium challenges and the DPH infusions were randomized

In six of the above experiments the solvent used to dissolve the diphenylhydantoin sodium was infused into the coronary circuit at the same infusion rates as those used during the study of DPH Under these conditions the solvent was not vasoactive nor did it affect myocardial contractile force

The data were statistically analyzed using the Student's t test modified for paired replicates

Results

Fig 1 shows that intracoronary administration of DPH produced a progressive fall in myocardial contractile force and coronary perfusion pressure both before and after ouabain It is also evident that the magnitude of the responses were not greatly different after ouabain The two highest infusion rates of DPH also reduced mean aortic pressure before and after ouabain

Intracoronary infusion of ouabain produced a progressive sustained increase in myocardial contractile force (Fig 2) Coronary perfusion pressure rose during the first 10 minutes of ouabain infusion and remained at this new high level during the last six minutes of the infusion period Upon termination of ouabain coronary pressure gradually fell toward the pre ouabain level Mean aortic pressure was not affected by ouabain

Ouabain did alter the response of the coronary vascular bed to potassium Before ouabain moderate hyperkalemia (elevation of ~ 2 5 mEq / L) reduced coronary perfusion pressure in five of eight experiments Following ouabain coronary perfusion pressure rose during the hyperkalemic challenge in six of eight experiments

Iatrogenic interruption of the myocardial conduction system

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In 1966 the prognosis for infants with transposition of the great arteries was significantly improved by the introduction of a new technique, the balloon atrial septostomy [1,2] By artificial enlargement of a pre existing patent foramen ovale blood could be shunted from one side of the heart to the other at the atrial level alleviating the critical condition of the infant and allowing for delay of the definitive surgical correction This procedure has since been used in the management of a variety of other cyanotic congenital cardiac lesions including total anomalous pulmonary venous return and pulmonary atresia with an intact ventricular septum [3,4] It is now widely employed and highly acclaimed[5-12] there have been but few reported complications [13-20]

Recently we have encountered a serious complication the nature of which has been well documented by postmortem examination including *serial sections of the conduction system* of the heart. The morphologic features observed at autopsy clearly correlate with the clinical course of the patient

Case presentation

The infant a full term Caucasian male weighed 3 400 grams at birth He did well until the third day of life when episodes of cyanosis and *respiratory distress* developed. A blowing systolic murmur was heard and the diagnosis of congenital heart disease was made He *was transferred to St. Christopher s Hospital* for Children on the eighth day of life On the evening of admission he underwent emergency cardiac catheterization which revealed transposition of the great vessels with a sizeable ventricular septal defect Upon completion of the diagnostic procedure balloon atrial septostomy was undertaken Following the first withdrawal of the balloon transient atrioventricular dissociation accompanied by severe bradycardia occurred. A second attempt to create an atrial septal defect by means of the balloon catheter was successful and uneventful

Later that night the pulse rate rose from 70 to about 170 beats per minute The following day cardiac arrest occurred on one occassion and the next day severe bradycardia developed followed by arrhythmia *episodes of bradycardia tachycardia* and premature ventricular contractions He died one and a half days after the procedure

Postmortem examination revealed transposition of the great arteries with a high ventricular septal defect. The membrane for closure of the patent and fenestrated foramen ovale had been completely torn transversely (Fig 1) There was also a complete vertical tear of the septal leaflet *of the tricuspid* valve and hemorrhage into and under the endocardium about that tear extending upward and backward toward the coronary sinus (Fig 1) All of the endocardial lining of the ventricular septal defect was disrupted rough dull hemorrhagic and covered with fibrin A single block of tissue containing the atrioventricular *node the Bundle* of His, and the right and left bundle branches was removed. Serial microscopic sections of the block in

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with earlier work[3,6,16,17] suggest that the myocardial depression is the result of a direct action of the drug on the myocardium rather than the result of an indirect effect mediated through extrinsic nerves, circulating hormones, and/or changes in venous return (Frank Starling effect) Although the mechanism of the myocardial depression is uncertain, the failure of ouabain to alter the response indicates that it does not result from a stimulating action of DPH on the myocardial cell membrane Na^+, K^+ ATPase *In vivo*[16] and *in vitro*[15,18] data support this conclusion

Summary

These studies suggest that the direct local effect of DPH is to relax coronary smooth muscle and depress myocardial muscle Further, the results indicate that neither the vascular nor myocardial effects of DPH are mediated through a stimulating action of the drug on the cell membrane Na^+, K^+ ATPase In contrast, the studies support the hypothesis that the vasodilator but not the cardiac depressant action of potassium results from a stimulating action of this ion on the sarcolemmal sodium potassium pump

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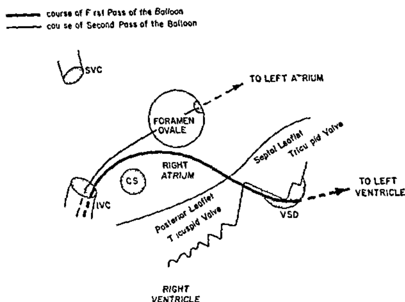


Fig 3. Diagrammatic representation of the internal aspect of the right side of the heart indicating the course of the balloon on each of the two passes. CS coronary sinus ostium of in right atrium IVC inferior vena cava ostium of in right atrium SVC superior vena cava ostium of in right atrium and VSD ventricular septal defect.

occurred. On the first pass of the balloon (Fig 3) after entering the right atrium via the inferior vena cava it did not, as was expected, pass through the foramen ovale into the left atrium Instead, it tilted downward passed through the tricuspid valve under its septal leaflet and thence through the ventricular septal defect into the left ventricle The balloon was inflated while in the lumen of the left ventricle and forcibly withdrawn It was during withdrawal in the inflated state through the ventricular septal defect that the balloon damaged not only the endocardial lining of the defect but also the surrounding myocardium and certain portions of the conduction system within it especially the upper portion of the left bundle It was this disruption of the origin of the left bundle which gave rise to the transitory atrioventricular dissociation. Fig 3 is a diagrammatic representation of the course of the balloon on each of the two passes

Fig 4 shows the results of those two passages the tear in the membrane of the foramen ovale the tear of the septal leaflet of the tricuspid valve and the hemorrhagic necrosis in the vicinity of the ventricular septal defect including damage to the conduction system

The fact that the right bundle was located at some distance from the defect and had thus re-

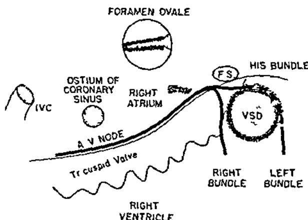


Fig 4 Diagrammatic representation (as in Fig 3) including the atrioventricular node, the common bundle, and the right and left bundle branches. The darker stippled areas about the ventricular septal defect at the edges of the tear in the membrane of the foramen ovale indicate hemorrhagic necrosis produced by the balloon. A V node atrioventricular node FS fibrous septum IVC inferior vena cava ostium of in right atrium and VSD ventricular septal defect.

mained intact permitted restoration of normal rhythm (Fig 4) The impulse originating in the sino-atrial node must have passed through the atrioventricular node down into the right ventricle by way of the common bundle and the right



Fig 1 The interior of the right atrium and ventricle following perfusion fixation. *A* Transverse tear through the membrane for closure of foramen ovale *B*, Vertical tear through the septal leaflet of the tricuspid valve *RAA* right atrial appendage RV right ventricle

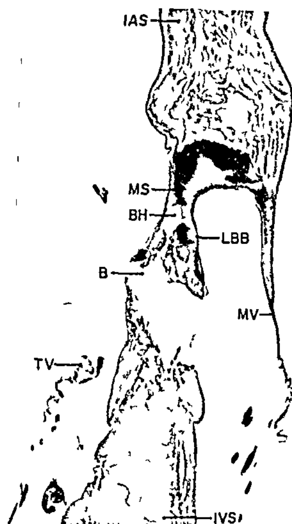


Fig 2. Coronal section through the interatrial, membranous, and interventricular septa showing the tear of the septal *leaflet of the tricuspid valve and destruction of tissues in the* vicinity of the ventricular septal defect produced by the balloon. At this level, the Bundle of His is seen giving rise to the left bundle branch the latter being completely interrupted. (Hematoxylin phloxine saffranin stain Magnification, × 15) *B destruction produced by balloon at the* margins of the septal defect BH Bundle of His IAS interatrial septum IVS interventricular septum LBB left bundle branch MS membranous septum MV mitral valve and TV tricuspid valve torn septal leaflet

plane were stained with hematoxylin, phloxine, and saffranin stain

Histologic study revealed that the torn edges of the membrane of the foramen ovale were covered with caps of fresh thrombus including red cells, fibrin, and fibroblasts Sections of the atrioventricular node showed nothing more than a few petechiae At the posterior margin of the ventricular septal defect however, massive hemorrhagic necrosis of the septal myocardium was evident. At one point this resulted in complete disruption of the Bundle of His as it gave rise to the left bundle branch in the upper portion of the ventricular septum The extent of destruction of the conduction system in this segment was considerable not only in the craniocaudal direction but also anteroposteriorly (Fig 2) Originally, we were unable to locate the right bundle Later, however, provoked by an inability to understand the spontaneous correction of atrioventricular dissociation, we reviewed all of the serial sections and located the right bundle, intact and undamaged, arising from the common bundle in an aberrant position almost immediately anterior to the descent of the common bundle below the fibrous septum it was far posterior to the endocardial and myocardial disruption about the septal defect.

Discussion

Retrospectively, reconstructing the events at septostomy, the following would appear to have

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bundle branch, and then proceeded across to the left ventricle

One of the precautions initially suggested by Rashkind and Miller[2] was that the pressure in the lumen of the chamber containing the balloon should be determined before its inflation and withdrawal By that means the operator can be assured that the balloon is correctly positioned in the left atrium That procedure requires the use of a catheter with a double lumen, one for pressure reading and the other for inflation of the balloon Because of the small size of the infant in this case, a single lumen catheter was employed The situation of the tip of the balloon at the apex of the pass was determined by fluoroscopy When a single lumen catheter is used guidance depends upon the operator s interpretation of the fluoroscopic image if the catheter seems to be directed straight across the heart, the balloon is presumed to lie in the left atrium if it is deflected downward however, the balloon is considered to be in the left ventricle In this instance its position was mistakenly interpreted as being in the left atrium whereas, in actuality it had passed through the ventricular septal defect into the left ventricle With its inflation and withdrawal on the first pass, the continuity of the conduction system at the level of the junction of the common bundle with the left bundle branch was disrupted Presumably the resultant atrioventricular dissociation was not permanent because of the aberrant origin of the right bundle branch that remained intact being at some distance from the site of trauma, thus permitting re establishment of near normal conduction

The second passage of the balloon was indeed through the anatomically (and physiologically) patent foramen ovale and succeeded in creating a larger atrial septal defect

Summary

This report documents the events which occurred during an attempt at balloon atrial septostomy The balloon passed forward from the right atrium through the tricuspid valve into the right ventricle and thence through the ventricular septal defect into the left ventricle where it was inflated During its withdrawal through the ventricular septal defect in the inflated state, it tore away the endocardial lining of the defect and elements of the conduction system deep to that, completely disrupting the junction of the common bundle and left bundle branch with resultant atrioventricular dissociation Serial histologic sections revealed that later correction of that dysrhythmia can be attributed to an aberrant origin of the right bundle branch at a considerable distance posterior to the defect and thus well removed from the site of damage

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spite of intravenous location of the pacing electrodes [1,2]

However thrombosis of these veins does occur with varying frequency following permanent placement of other foreign bodies within them The ventricular venous shunts used in the management of hydrocephalus frequently result in occlusion of jugular or innominate veins or superior vena caval obstruction [3] This may be partially attributed to increased frequency of sepsis to intimal trauma from the catheter tip and to the small diameter of the vessels in children It is postulated that rapid endothelialization occurs around the pacing electrodes which ordinarily prevents the development of thrombosis and thromboembolism [4]

A hypothesis to explain the thrombosis of the innominate veins in our patient is as follows clotting may have occurred in the short, blind end of the ligated cephalic vein The clot may have propagated centrally to the subclavian and innominate veins Partial obstruction of the subclavian vein by the electrode and the stasis in the subclavian vein secondary to congestive heart failure may also have been contributing factors. Initially the patient probably had complete occlusion of the right innominate vein and partial obstruction of the left innominate vein which would explain the difference in severity of signs and symptoms of the two extremities The superior venacavogram at five months following the onset of symptoms and following treatment with anticoagulation therapy showed partial resolution of the thrombus and recanalization of these vessels, and the development of collaterals This explains the spontaneous disappearance of the symptoms.

The use of the cephalic veins for the introduction of transvenous pacing electrodes offers several advantages (1) only one incision is required to insert the pacing electrodes and to create the pocket for the pulse generator, (2) secure fixation of the electrodes and avoidance of risk of electrode displacement. If the electrodes are placed through external or internal jugular veins, the neck movements may affect their position (3) The relatively easy dissection for exposing the cephalic vein because of its constant anatomic relationship to the delto pectoral groove and its superficial location, and (4) the decreased chances of air embolization in comparison to the internal jugular venous route



Fig 1 Superior venacavogram showing partial occlusion of the innominate veins and superior vena cava Reflux of dye up in the internal jugular vein and large collateral veins is also seen

Nonetheless use of the cephalic vein to insert the pacing electrodes has certain disadvantages There is a definite increased risk of venous thrombosis when the external jugular or cephalic veins are used as a route for superior vena caval catheterization Nordlund and Thoren[5] reported an incidence of venous thrombosis of almost five per cent, including superior vena caval obstruction Occasionally the cephalic vein may be of too small a caliber and too poor quality to accept the pacing electrodes

Benign innominate venous occlusion or benign superior vena caval obstruction rarely require surgical intervention. Usually elevation of the head to reduce facial and cerebral edema, diuretics and anticoagulants are all that are necessary until increased venous pressure and obstructive venous flow are relieved spontaneously by the development of collateral venous channels Resolution of thrombus and recanalization of vessel lumen also play important roles in reconstitution of normal venous flow Intravenous heparin in adequate dosages to prolong the clotting time to two and a half times normal should be instituted as soon as the diagnosis is made Though rare occasionally pulmonary embolization may occur from primary subclavian, axillary or superior vena caval

Innominate venous thrombosis A rare complication of transvenous pacemaker electrodes

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Oteen, N C

Thrombotic occlusion of axillary, subclavian, or innominate veins, or of superior vena cava due to transvenous endocardial pacing electrodes is an extremely rare occurrence Recently, we encountered a patient with occlusion of the innominate veins probably due to transvenous pacing electrodes, and were able to manage him successfully without surgery

Case report

This 57 year old male was admitted on Oct. 30 1972 to another hospital with history of syncopal attacks for 20 hours prior to admission In the past, he has had an inferior myocardial infarction Physical examination on admission revealed a blood pressure of 120/80 mm Hg pulse 50 per minute and signs of congestive heart failure Electrocardiogram showed evidence of old inferior wall myocardial infarction and sinus bradycardia with a rate of 45 to 60 per minute Moderate cardiomegaly was seen on chest X ray Blood chemistries were normal. Twenty four hours after admission he developed intermittent complete heart block. He was transferred to the Veterans Administration Hospital Oteen on Nov 2 1972 and underwent the placement of a permanent demand Medtronic transvenous pacemaker through the right cephalic vein. He did well postoperatively and for four months following surgery when he developed right sided headaches swelling of the right side of the face neck and right arm He had difficulty seeing from the right eye because of edema of the eyelid. Examination at this time showed the patient to be apprehensive and in acute distress with pain Blood pressure was 130/80 mm Hg and pulse rate of 72 per minute and regular There was obvious swelling of the right side of the face and neck The diameter of the right arm was 2 5 cm greater than that of the left arm There were prominent engorged veins over the right upper arm and the pectoral region The right external jugular vein was distended and tender The right carotid pulse was barely palpable because of edema of the neck The blood chemistry determinations were normal Electrocardiogram showed a normal functioning demand pacemaker and evidence of an old inferior wall myocardial infarction

A clinical diagnosis of occlusion of the right innominate vein was made and the patient was placed on intravenous heparin in dosages of 50 mg every four hours and Coumadin was also begun. Within 72 hours, the swelling of the face became less, tenderness and distention of the jugular vein improved, and the headaches disappeared. Heparin therapy was discontinued after one week After two weeks swelling of the face and neck tenderness and distention of jugular vein and distention of veins over the neck, pectoral region, and arm disappeared. However he continued to have swelling of the right arm. A superior venocavogram nine months following surgery showed partial occlusion of both innominate veins and the superior vena cava and evidence of collateral venous channels (Fig 1) At follow up one year after operation the patient was almost asymptomatic However his right arm was still larger than the left. Coumadin therapy has been continued.

Discussion

Endocardial pacing electrode complications unique to their intracavitary location include cardiac perforations, incarceration of the electrodes within the heart, intravascular migration of severed electrodes, repeated displacements of electrodes from the original contact points and an increase of pacing threshold due to fibrosis around the electrode tip It is interesting to note that rarely do thrombosis or occlusion of the innominate vein or superior vena cava occur in

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spite of intravenous location of the pacing electrodes.[1,2]

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thrombosis[6,7] To avoid this serious complication, we believe that long term anticoagulation therapy in this group of patients is indicated

Summary

Thrombosis and occlusion of innominate veins or superior vena cava are extremely rare, but may be a major complication of transvenous pacing electrodes These patients have the usual signs and symptoms of superior vena caval syndrome and should be managed with anticoagulation therapy

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Clinical-pathologic conference

Cyanotic congenital heart disease and sudden death

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Case presentation

W M BCH No 55 69 89 and JHH No 729791 was a 17 year old male who was admitted to the Baltimore City Hospitals (BCH) on Oct 30 1969 after he had collapsed suddenly at home

The patient had congenital heart disease (CHD) which was known since the age of four months He was cyanotic at birth a murmur was described at the age of four months and marked clubbing was described at the age of 27 months A chest x ray showed cardiomegaly increased pulmonary vascularity and a prominent pulmonary conus The electrocardiogram (ECG) showed right axis deviation biventricular hypertrophy and P waves of right atrial enlargement

He was retarded in growth and development and had frequent respiratory infections At four years of age right heart catheterization and angiocardiography were performed because of clinical deterioration manifested by exercise intolerance increasing cardiomegaly and increasing cyanosis with a hematocrit of 78 The catheter entered the aorta from the right ventricle The right ventricular pressure was elevated to systemic levels There was a step up in oxygen of four volumes per cent (vol %) in the right ventricle consistent with left to right shunting at ventricular level Angiography with injection of contrast material into the right ventricle demonstrated increased pulmonary vascularity and simultaneous filling of the aorta and the pulmonary artery

A few months later an atrial septal defect was created surgically Following this procedure there was an increase in exercise tolerance a decrease in cyanosis and the hematocrit fell to 63 At the age of seven years repeat catheterization demonstrated that there was no gradient across the pulmonic valve and no significant right to left shunt at the atrial level The pulmonary artery was entered from the right ventricle There was an oxygen step up of 7 vol % from the right atrium to the right ventricle It was not clear how much of this left to right shunt was across the surgically created atrial septal defect

The patient attended school with moderate limitations in activity His hematocrit rose slowly to preoperative values Repeat studies at the ages of 8 and 9 years showed that, when contrast material was injected into the left ventricle there was preferential filling of the pulmonary artery and, when injection was made into the right ventricle both great vessels filled simultaneously (Figs 1 and 2)

At the age of 15 years he was admitted for elective phlebotomy because of headaches and blurring of vision with an hematocrit of 78 At this time note was made of episodes of pleuritic left sided chest pain as well as substernal pain with effort. Physical examination described deep cyanosis and marked clubbing The blood pressure was 105/80 mm. Hg in both arms. The femoral artery pulses were normal The pulse rate was 85 beats per minute and regular The heart was enlarged to the anterior axillary line with a

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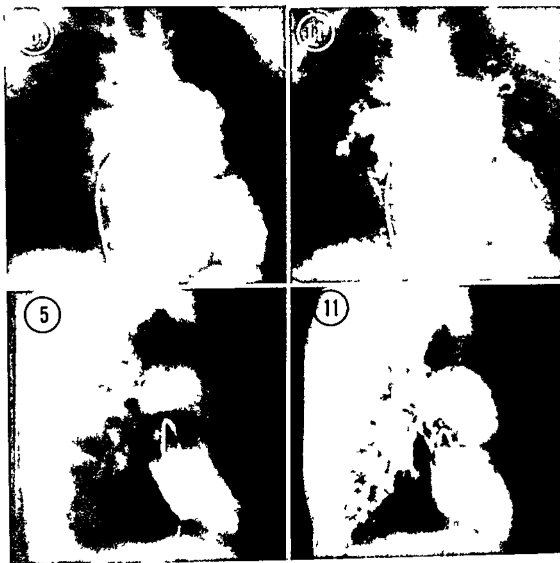


Fig 1 Selected simultaneous biplane angiograms AP and lateral views. The catheter has been passed from the right atrium through the surgical ASD into the left atrium and then into the cavity of a left, posterior ventricle There is excellent visualization of a large pulmonary artery (PA) with increased pulmonary vascularity Poor filling of the aorta is noted The ventricle has the characteristics of an anatomic left ventricle

prominent right ventricular heave The second sound was easily palpable in the pulmonic area and there was a prominent ejection click which disappeared during inspiration The second sound was narrowly split with an increased second component. A Grade II/VI apical systolic ejection murmur and a Grade I/VI short diastolic murmur were described Chest x ray showed moderate cardiomegaly which was predominantly right ventricular and marked dilation of the undivided pulmonary artery and of the central pulmonary arteries with peripheral tapering (Fig 3) The ECG showed right axis deviation, right ventricular hypertrophy, probable left ventricular hypertrophy, and P waves of right atrial enlargement (Fig 4) The hematocrit was 78 with a normal white count and differential count Urinalysis gave a 4+ test for protein and urinary excretion of protein was 1 5 Gm per 24 hours The uric acid was 10 7 mg per cent with a serum urea nitrogen (SUN) of 20 mg per cent and a creatinine of 1 3 mg per cent Serial phlebotomies with saline replacement reduced his hematocrit to 64 and the patient was discharged on digitalis

During the next two years the patient was apparently stable The night before his final hospital admission the patient was seen complaining of a sore throat. The next morning he collapsed in the bathroom and was brought to the emergency room in respiratory and cardiac arrest. Resuscitative maneuvers including electrical defibrillation, restored a cardiac rhythm but an audible heart beat or palpable pulse never returned The hematocrit was 77 The ECG initially showed ventricular fibrillation followed by



Fig 2. Selected PA and lateral angiograms with injection of contrast into a trabeculated anterior ventricle anatomically a right ventricle Both great vessels fill well and simultaneously Note that the pulmonary artery is anterior and to the left of the aorta and that the aortic and pulmonary valves are at the same level.

a supraventricular tachycardia and, terminally sinus bradycardia Resuscitative efforts were abandoned after two hours

Clinical discussion

I am going to approach the clinical discussion of this patient from each of three aspects (1) the etiology of his heart disease (2) the contribution to the total clinical picture of complications of cyanotic CHD and (3) the mode of his sudden and unexpected death

Table I is a classification of CHD modified after Kanjuh and Edwards, which provides a convenient approach to the differential diagnosis of CHD utilizing information obtained from clinical data the chest x ray and the ECG

This patient was cyanotic *since birth*, early chest x rays showed an *increase* in pulmonary vascularity and ECG s showed right ventricular hypertrophy This information alone permits us to define the nature of the possible anatomic defects present The fact that cyanosis was present since birth is good evidence against an isolated abnormal communication between the left and right heart or between the aorta and the pulmonary artery with shunt reversal producing cyanosis Shunt reversal usually occurs later when pulmonary hypertension develops or changes in pulmonary arterial vessels produce a critical rise in pulmonary arterial resistance Before excluding those conditions characterized by decreased or normal pulmonary arterial vascularity with cyanosis we must consider the possibility that what was interpreted as in creased pulmonary vascularity actually represented enlarged collateral bronchial arteries due



Fig 3 Chest x ray taken at the age of 15 years There is cardiomegaly predominantly right ventricular The main and central pulmonary arteries are large with peripheral tapering consistent with the vascular changes of pulmonary hypertension

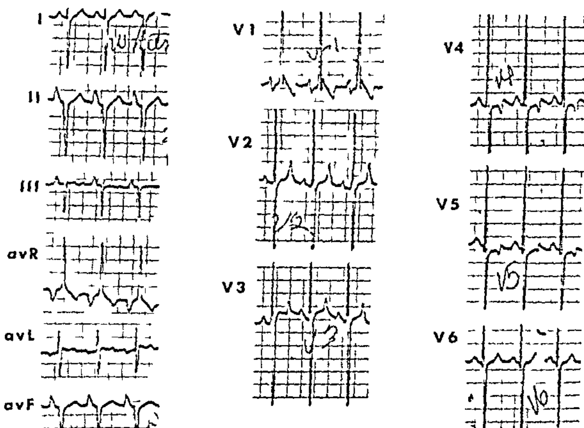


Fig 4 ECG at the age of 15 showing right axis deviation right ventricular hypertrophy probable left ventricular hypertrophy and P wave changes of right (and perhaps left) atrial enlargement (Retouched)

to severe pulmonary outflow obstruction, as in pulmonary atresia with tetralogy of Fallot, or a pseudotruncus

The presence of clinical and electrocardiographic evidence of right ventricular hypertrophy and the presence of increased pulmonary vascularity exclude with some degree of confidence, the possibilities listed in Table I under section IIB Likewise, there is no evidence for isolated pulmonary stenosis coarctation of the aorta or aortic outflow obstruction

On the basis of history, chest x ray, and ECG s,

we have narrowed down the possibilities to a manageable number namely (1) a single ventricle (*cor triloculare biatriatum*) without pulmonic stenosis (2) origin of both great vessels from the right ventricle without pulmonary stenosis, (3) complete transposition of the great vessels (4) total anomalous pulmonary venous return with an intracardiac shunt, and (5) tetralogy of Fallot with pulmonary atresia and increased bronchial arterial flow (pseudotruncus)

Let us now turn to the data obtained from cardiac catheterization At the first catheterization the aorta was entered from the right ventricle This could mean a single ventricle origin of both great vessels from the right ventricle a complete transposition or tetralogy of Fallot Angiography demonstrated *simultaneous* filling of the pulmonary artery and the aorta with increased pulmonary arterial flow This information excludes tetralogy of Fallot.

Following palliative surgery further studies were indicated to better define the relationship between the pulmonary artery and the aorta and to determine the anatomy of the ventricular septum It would appear that there are two ventricles and pulmonary stenosis was excluded The fact that the main pulmonary artery appears to be in a near normal position to the left of and anterior to the aorta rather than being posterior and to the right of the aorta is against complete transposition as is the fact that both great vessels filled well after injection of contrast material into the right ventricle[3] It appears that the aortic and pulmonic valves are at the same level. The evidence thus far leaves little question that both great vessels originate from the right ventricle and that there is a ventricular septal defect (VSD)[3,4]

One other observation is important The pulmonary artery filled preferentially when dye was injected into the left ventricle When both great vessels originate from the right ventricle circulation depends upon a VSD The VSD may be located above or below the *crista supraventricularis*. When it is located below the *crista supraventricularis* (Type I of Neufeld[4]) left ventricular blood goes predominantly out the aorta and the circulation resembles that of a VSD When the VSD is *above* the *crista supraventricularis* (Type II) right ventricular blood tends to go out the aorta and left ventricular blood out the pulmonary artery In Type II therefore cyanosis is more severe Type II double outlet right ventricle is synonymous with the Taussig Bing anomaly[5] The angiographic findings and the profound cyanosis lead me to the conclusion that this patient had the Taussig Bing anomaly

The patient had severe polycythemia

Table I

I Increased prominence of pulmonary arterial vessels
- A Without cyanosis
  1. Atrial septal defects
  2. Ventricular septal defects
  3. Left ventricular right atrial fistula
  4. Communication between coronary artery and coronary sinus or right atrium
  5. Anomalous pulmonary venous drainage into *systemic vein or right atrium*
  6. Patent ductus arteriosus
  7. Aortico pulmonary window
  8. Accessory or anomalous coronary artery from pulmonary trunk
- B With cyanosis
  1. Eisenmenger syndrome
  2. Total anomalous pulmonary venous return
  3. *Single ventricle without pulmonary stenosis*
  4. Origin of both great vessels from right ventricle without pulmonary stenosis
  5. Complete transposition of great vessels

II Decreased or normal prominence of the pulmonary arterial vessels with cyanosis
- A With right ventricular hypertrophy
  1. Tetralogy of Fallot
  2. Pseudotruncus
  3. Origin of both great vessels from right ventricle with pulmonary stenosis
  4. Single ventricle with pulmonary stenosis
  5. Persistent truncus arteriosus with pulmonary stenosis
  6. Pulmonary stenosis with intact ventricular septum and trans atrial right to left shunt
  7. Pulmonary atresia with intact ventricular septum
- B Without right ventricular hypertrophy
  1. Tricuspid atresia
  2. Ebstein s malformation of the tricuspid valve
  3. *Communication of superior or inferior vena cava* with left atrium
  4. Pulmonary arteriovenous fistula

III Normal pulmonary arterial vessels without cyanosis
- A With right ventricular hypertrophy
  1. Pulmonic stenosis
  2. Peripheral pulmonary arterial stenosis
- B With left ventricular hypertrophy
  1. Coarctation of the aorta
  2. Stenosis in region of aortic valve

IV Prominent pulmonary arterial and venous vessels with right ventricular hypertrophy and without cyanosis—pulmonary venous obstruction



Fig 3 Chest x ray taken at the age of 15 years. There is cardiomegaly predominantly right ventricular The main and central pulmonary arteries are large with peripheral tapering consistent with the vascular changes of pulmonary hypertension

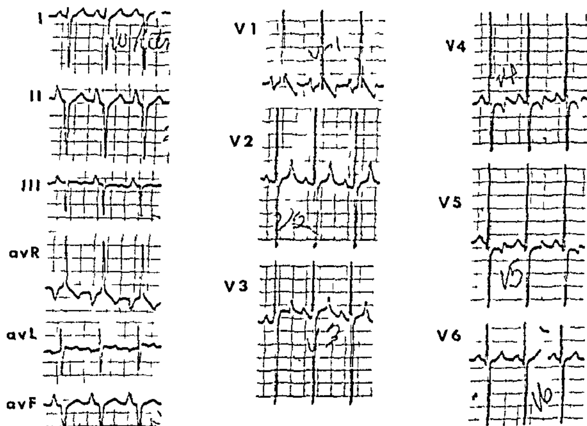


Fig 4 ECG at the age of 15 showing right axis deviation right ventricular hypertrophy probable left ventricular hypertrophy and P wave changes of right (and perhaps left) atrial enlargement (Retouched)

to severe pulmonary outflow obstruction, as in pulmonary atresia with tetralogy of Fallot, or a pseudotruncus

The presence of clinical and electrocardiographic evidence of right ventricular hypertrophy and the presence of increased pulmonary vascularity exclude with some degree of confidence, the possibilities listed in Table I under section IIB Likewise, there is no evidence for isolated pulmonary stenosis coarctation of the aorta or aortic outflow obstruction

On the basis of history, chest x ray and ECG's

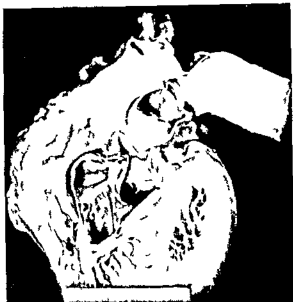


Fig 5 Coronal section of the heart. The right ventricular cavity gives rise to the aorta on the left and the pulmonary artery on the right The pulmonary artery straddles a large interventricular septal defect so that fragments of the left ventricular mural thrombus (shown in the interstices of the left ventricle) were carried into the main pulmonary artery



Fig 6 Comparison of the hypercellular enlarged glomeruli in the present patient (*A*) with those from a patient of the same age who died following an auto accident (*B*) Both photographs have been taken at the same magnification (×165 hematoxylin and eosin.)

Sudden death presumably due to an arrhythmia is well recognized in patients with primary idiopathic pulmonary hypertension It is possible that an arrhythmia caused sudden death perhaps produced by relative myocardial ischemia in the presence of increased myocardial oxygen need due to fever secondary to infection I think that acute MI is unlikely although I have seen acute infarction in the Taussig Bing anomaly with anomalous origin of the coronary arteries

There appears to be an increased incidence of pheochromocytoma in patients with cyanotic CHD[20] Sudden death in patients with pheochromocytoma due to cerebrovascular accidents, MI shock pulmonary edema or arrhythmia has been reported.[21-23] This patient never had hypertension recorded and, although hypertension in pheochromocytoma may be sporadic I cannot make this diagnosis in the absence of hypertension in a closely followed patient

The Taussig Bing anomaly is occasionally associated with coarctation of the aorta and the possibility of dissection or rupture of the aorta complicating coarctation should be mentioned. In view of the absence of hypertension the presence of normal femoral artery pulses and no decrease in hematocrit when he presented with cardiac arrest I think these possibilities can be excluded.

I think that this patient died of a thromboembolic event The findings of increased pulmonary vascular resistance pleuritic chest pain and sudden death strongly favor massive pulmonary embolism It is well known that small pulmonary emboli often precede massive fatal embolism a fact of tremendous therapeutic importance

In summary I believe this patient had origin of both great vessels from the right ventricle of the Taussig Bing variety and that he died of massive pulmonary embolism Considering the fact that the pulmonary artery filled predominantly from the left ventricle the possibility of paradoxical embolism across the surgically created ASD is intriguing

Polycythemia is the major factor contributing to complications of cyanotic CHD[6] An increase in the number of circulating red blood cells produces *increased viscosity*, predisposing to thromboembolic events such as cerebrovascular thrombosis, pulmonary arterial thrombosis, and pulmonary and systemic embolization Paradoxically, bleeding may be a problem and several coagulation defects including thrombocytopenia, low fibrinogen, low prothrombin, and poor clot retraction have been described[7,9] Late in this patient s course he developed symptoms suggesting that increased viscosity was producing circulatory insufficiency and perhaps frank thromboembolic events were occurring He complained of headaches and blurring of vision, suggesting cerebral ischemia In addition the patient complained of pleuritic chest pain and pulmonary infarction, due either to emboli or *in situ* thrombosis, is a likely possibility Multiple pulmonary arterial thrombi were first described in cyanotic CHD by Rich[14] in a patient with tetralogy of Fallot and the report of a patient with a double outlet right ventricle by Taussig and Bing[5] described organizing thrombi in the pulmonary arteries and intimal proliferation which narrowed the pulmonary arterioles

The possibility that a cerebral abscess was producing headaches and visual disturbances should be considered Cerebral abscess is a common complication of cyanotic CHD and its frequency increases with age Abscess is thought to be due to the fact that venous blood bypasses the normal filtering action of the lungs so that arterial bacteremia occurs without endocarditis Previous cerebral infarction may predispose to abscess formation[10,13] Fever and leukocytosis were not present and his subsequent course does not suggest brain abscess The possibility that his sudden death was due to rupture of a cerebral abscess cannot be excluded

The patient had another type of chest pain—substernal pain with effort This sounds like angina Coronary artery disease due to atheroma is quite rare in cyanotic CHD In fact the coronary arteries of patients with cyanotic CHD are remarkably large and free of narrowing, a compensation for the decreased oxygen carrying capacity of arterial blood requiring a chronic increase in coronary flow to maintain nourishment of hypertrophied ventricular muscle Pain resembling angina is often seen in patients with severe pulmonary hypertension due to any cause, particularly in patients with mitral stenosis, primary idiopathic pulmonary hypertension, and CHD with the Eisenmenger's syndrome The cause of the anginal like pain is not clear Some feel that the pain is due to myocardial ischemia due to inadequate coronary perfusion due to a limitation in cardiac output. Others feel that the pain is due to distention of the pulmonary artery due to an attempt to increase pulmonary flow in the presence of high pulmonary arterial resistance[15,17] It is conceivable that either mechanism may be operative in a given patient.

Physical examination two years prior to death suggested that pulmonary arterial resistance had increased A palpable pulmonic closure sound, a prominent ejection click which disappeared with inspiration, a narrowly split second sound, and a murmur consistent with pulmonary valve incompetence all point to a severe increase in pulmonary arterial resistance This increase in pulmonary vascular resistance suggests progressive obliterative disease of the pulmonary arterial vessels consistent with increasing polycythemia with further reduction in pulmonary flow

Before turning to the problem of the patient's sudden death, I would like to discuss two more aspects of this patient's disease Hyperuricemia was noted without clinical gout. An elevated uric acid is seen in polycythemia due to any cause Podagra is rare in cyanotic CHD and is usually seen only in the adult.[18] The second point is the significant proteinuria Proteinuria in cyanotic CHD has been observed and associated with renal mesangial lesions[19]

In spite of a number of reasons which could cause death in this patient, we must explain why death occurred suddenly and unexpectedly Sudden death has but a few causes, and for all practical purposes is due to asphyxia or some cardiovascular catastrophe such as hemorrhage rupture of a vessel pulmonary embolism an arrhythmia, or acute myocardial infarction

This patient was seen within 24 hours of his death complaining of a sore throat Acute tonsillitis with a retropharyngeal abscess may produce acute upper airway obstruction and the abscess may rupture producing aspiration and asphyxia with sudden death Evidence for this should have been obvious when the patient presented and resuscitative efforts which included tracheal intubation were performed.

parent that similar but smaller nodules were distributed along the entire abdominal sympathetic chain and corresponded to enlarged sympathetic ganglia. Histologically these structures had the appearance of paraganglionic chromaffin adenomas although hyperplasia may be a more appropriate designation (Fig 8) Zenker fixed material was not available for the Henle reaction but prolonged formalin fixation resulted in a deep mahogany brown color suggestive of high catecholamine content.

Tumors of the chromaffin system occur with unusual frequency in patients with cyanotic CHD although their functional significance remains obscure [9] We have observed similar tumors in patients with other forms of chronic anoxia associated with marked polycythemia and have questioned whether this reaction may be implicated with the increased erythropoiesis characteristic of these states It is conceivable that these minor degrees of chromaffin hyperplasia occur in many patients with prolonged anoxia but unless carefully searched for may easily be overlooked.

In summary this patient had a classic Taussig Bing malformation of the heart with pulmonary hypertension and polycythemia Because of the peculiar anatomic configuration of the great vessels a mural thrombus in the left ventricle resulted in massive terminal pulmonary embolization and death

DR. VOIGT It is interesting to speculate on the cause of mural thrombosis of the left ventricle in this patient This is an unusual finding in the absence of ventricular aneurysm acute MI or severe congestive failure with ventricular dilation I have seen mural thrombosis in the *right* ventricle in patients with severe pulmonary hypertension once in a patient with idiopathic primary pulmonary hypertension and in another patient with pulmonary hypertension due to pulmonary alveolar microlithiasis In the latter patient the clot propagated into the main pulmonary artery through the pulmonic valve producing almost total obstruction In the patient under discussion the left ventricle had only one outlet, through the VSD and the left ventricle was pumping blood into the pulmonary artery The mechanism of mural thrombosis may be similar to that which occurred in the right ventricle with pulmonary hypertension It is conceivable that incomplete emptying of the ventricle due to increased pulmonary vascular resistance resulted in stagnation of blood within the ventricular chamber producing thrombosis which was perhaps encouraged by the polycythemia

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Fig 7 Angiomatoid malformation of a pulmonary artery showing extrusion of vasoformative tissue through a mural defect Serial sections indicated that these vascular channels were in communication with the pulmonary alveolar capillaries (×64 hematoxylin and eosin)



Fig 8 Section through the capsule of the largest paraganglionic tumor Polyhedral cells on the left are arranged around a rich sinusoidal vascular network. To the right of the fibrous capsule retroperitoneal fat exhibits fetal atrophy a response possibly related to hormonal activity (×165 hematoxylin and eosin.)

Postmortem findings

An autopsy was performed 7 hours after death and revealed a small but well developed, black male with clubbing of the fingers and generalized cyanosis The heart weighed 540 Gm most of the enlargement being attributable to right ventricular hypertrophy A Taussig Bing cardiac malformation was confirmed The aorta was dextrorotated arising exclusively from the right ventricle and the pulmonary artery was levopositioned, straddling a large interventricular septal defect (Fig 5) The surgically created Blalock Hanlon interatrial defect was widely patent The major coronary arteries arose from the aortic root and exhibited no significant arteriosclerosis Some intimal thickening was present in the epicardial and intramyocardial arterial branches and the myocardium contained many small interstitial perivascular scars A large recent but organizing, mural thrombus occupied the left ventricular apex and fragments had embolized into the over riding pulmonary artery resulting in massive terminal pulmonary arterial occlusion

The kidneys were enlarged and microscopically were characterized by hypertrophied hypercellular glomeruli in which there was a striking proliferation of mesangial cells (Fig 6) The juxtaglomerular apparatus was also hyperplastic These glomerular alterations are characteristic of patients with certain forms of CHD but have also been observed in individuals subjected to longstanding anoxia from other causes.[19] The functional significance of this phenomenon has not as yet been established.

In addition to evidence of episodic major pulmonary emboli there was marked arteriosclerosis of the main pulmonary vasculature, a morphologic indicator of significant pulmonary hypertension Looking further along the pulmonary vascular tree many of the peripheral pulmonary arteries exhibited a peculiar arteritic lesion characterized by the intraluminal proliferation of vasoformative tissue with mural lysis and extravascular herniation to form paravascular angiomatoid structures (Fig 7) On serial section these angiomatoid networks appeared to empty directly into the peripheral pulmonary capillary bed. The physiologic significance of these peculiar malformations is not entirely clear but perhaps they constitute a compensatory mechanism for certain forms of pulmonary hypertension In other words, these vascular proliferations may protect the delicate peripheral pulmonary capillary bed from excessive pressures at the same time maintaining a peripheral pulmonary blood flow

Finally, at autopsy a large 6 by 6 cm tumor like mass was identified near the hilum of the right kidney On further dissection it became ap

Arterial pulse waves and velocity and systolic time intervals in diabetic children

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Lax and Feinberg[1,2] were the first to describe abnormalities of the digital arterial pulse wave in children with diabetes mellitus This observation suggested that there may be an abnormality of the arterial system at a young age in patients with diabetes Woolam and his associates[3] found an increase in arterial pulse wave velocity in diabetic patients as compared to normal individuals in all age groups including children under 10 years of age Since an increase in pulse wave velocity is seen in the presence of atherosclerosis[4,5] Woolam ascribed his results to the early development of atherosclerosis in diabetic children

Woolam s observations were extended further by Gunn and his associates[6] who measured pulse wave velocity in potential diabetic subjects using siblings parents and children of diabetic patients An abnormal prednisone glucose test was used as the criterion of potential diabetes in adults and parental diabetes as the criterion in the subjects under age 20 Although the groups were small an increase in pulse wave velocity was noted in the prepubescent children of diabetic patients Katz and co workers[7] correlated pulse wave velocities and small vessel disease as observed in biopsies of gingiva and ear lobes While confirming the presence of an increased pulse velocity in diabetic children no correlation was found between this change and the presence or severity of small vessel disase as seen in the biopsy specimens.

Pulse wave velocity is determined primarily by the elasticity of the arterial walls the stiffer the wall the greater the velocity The velocity also is dependent to a lesser extent on the velocity of blood flow which in turn is related to left ventricular contractility and the velocity of ejection Since the vascular lesion in diabetes mellitus affects the microcirculation primarily one would not expect to find atherosclerosis of such a degree as to affect pulse wave velocity significantly in children The observations quoted above therefore, are surprising The present study was designed to confirm the presence of large artery abnormalities in diabetic children and to assess whether the increase in velocity could be due to an increase in ventricular contractility and consequent velocity of ejection using systolic time intervals as an index of the latter An additional purpose was to determine whether the abnormalities in the shape of the pulse wave previously observed in the digital arteries[1,2] were also present in larger and more central arteries.

Methods

The subjects for this study include 39 children with stable diabetes mellitus from the ages of seven through 18 seen in the outpatient department of the Children s Hospital of the District of Columbia In addition 27 normotensive healthy children in the same age group with no known family history of diabetes were used as controls.

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Table I Pulse wave velocity indices

Artery	Normals, mean ± S D (M/sec)	Diabetics mean ± S D (M/sec)	Difference of means (M/sec)	t	p*
Brachial	5 5 ± 0 9	6 1 ± 1 3	+0 6	2 04	<0 025
Aortic	5 4 ± 0 7	6 1 ± 1 0	+0 7	2 83	<0 005

*The probabilities are given for a one tailed test.

influenced by heart rate In patients with A V block the pulse wave velocity does not change significantly when the heart is paced at differing rates[18]

Student s t test was used to test the significance of the differences between the normal and diabetic children

Pulse wave velocity indices Two pulse wave velocity indices were computed for each subject, the brachial and the aortic The brachial velocity index was calculated by dividing the upper arm length by the time difference between the foot of the carotid and the foot of the brachial pulse The aortic velocity index was calculated by dividing the trunk length by the time difference between the carotid and the femoral pulses

Pulse wave contours Pulse wave contours were analyzed with the use of amplitude ratios and time intervals of features of the pulse wave as shown in Fig 1 which have been previously described.[11] These included the following time intervals and amplitude ratios

- $F F_2$ = Time interval between the beginning and the end of the pulse wave cycle
- F I = Time interval from the beginning of the pulse wave to the incisura
- F P = Time interval from the beginning of the pulse wave to its peak.
- I/D = The amplitude ratio of the incisura relative to the midpoint of the dicrotic wave
- I D = The time interval from the incisura to the mid point of the dicrotic wave
- I/P = The amplitude ratio of the incisura relative to the peak
- P I = The time interval from the peak of the pulse wave to the incisura

Since the carotid pulse waves of most of the children in this study exhibited only the first systolic maximum, no attempt was made to identify the second systolic maximum[11] The time intervals which were correlated significantly with heart rate were corrected for heart rate by means of the regression equations obtained from

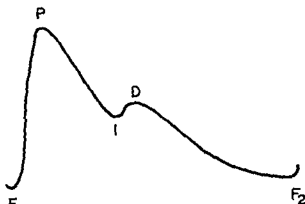


Fig 1 Location of features identified in the carotid and brachial pulse waves.

the normal children rather than dividing the cycle length as previously described.[11]

Systolic time intervals The following time intervals were calculated.

- $Q S_2$ = Time interval from the beginning of the QRS complex in the ECG to the onset of the second heart sound on the phonocardiogram
- $S_1 S_2$ = Time interval between the onset of the first heart sound and the onset of the second heart sound.
- LVET = Left ventricular ejection time the time interval between the onset of the upslope of the carotid pulse and the incisura
- $S_2 I$ = The time interval between the onset of the second heart sound and the incisura of the carotid pulse wave
- PEP = $(Q S_2)$–LVET = The pre ejection period, represented by the time interval from the onset of QRS in the ECG to the onset of the second heart sound minus the left ventricular ejection time
- $Q S_1$ = The time interval between the onset of QRS in the ECG and the onset of the first heart sound.
- ICT_2 = The late phase of isovolumic contraction, calculated by subtracting LVET from the time interval $(S_1 S_2)$

A correction for heart rate was made using normal regression equations for those systolic time intervals which showed significant dependance on cardiac rate

The average age for all diabetics was 13 8 years and for controls 13 3 years The average heart rate for the diabetics was 84 2 per minute and 75 4 per minute for the controls There was no significant difference in blood pressure between the two groups of subjects Systolic blood pressure averaged 112 2 ± 8 5 mm Hg (S D) in the normal subjects and 113 9 ± 10 5 mm Hg in the diabetic patients Diastolic blood pressure averaged 70 3 ± 8 7 mm Hg in the normal group and 72 9 ± 10 3 in the diabetic group

The average known duration of diabetes was 4 3 years, with a range of one week to 11 5 years All patients were receiving insulin either as NPH or Lente given alone or in combination with regular or semi Lente insulin The doses of insulin ranged between 14 and 80 units per day the average being 51 units All patients also received an antidiabetic diet

The quality of the control of the diabetes was evaluated with the use of the method of Gamstorp and associates[8] Good control indicated that the urine was free of glucose and acetone at least 75 per cent of the time the fasting blood glucose was consistently below 200 mg per 100 ml ketoacidosis was present only during illness hypoglycemic reactions were absent or rare and growth and development were normal Fair control indicated that the urine was free of glucose or acetone 50 to 75 per cent of the time, the fasting blood glucose always was below 250 mg per 100 ml and there were occasional hypoglycemic reactions or ketoacidosis "Poor control indicated that the patient had glycosuria or acetonuria more than 50 per cent of the time, the fasting blood sugar usually was above 250 mg per 100 ml and there were repeated hypoglycemic reactions or ketoacidosis On the basis of these criteria 18 of the diabetic patients were classified as being under good control,' 18 under 'fair control, and three under poor control

After the blood pressure had been measured in the sitting position the patients were placed supine on an electrically grounded stretcher Simultaneous tracings of the electrocardiogram (ECG), phonocardiogram, and externally recorded pulse waves were recorded on magnetic tape by means of Hewlett Packard amplifiers A standard phonocardiogram microphone was used and was placed over the second left thoracic interspace at the sternal border External transducers previously described[9] were placed over the right carotid artery 5 cm above the right sternoclavicular joint and over the right brachial artery pulsation at the antecubital fossa Four 10 second recordings of the ECG, phonocardiogram, and carotid and brachial pulse waves were made The transducer used for the brachial pulse was placed over the right femoral artery just distal to the inguinal ligament and four additional recordings were taken

In addition, the distance from the site of the carotid transducer to the site of the brachial transducer (arm length) and from the carotid site to the site of the femoral transducer (trunk length) were measured. In the diabetic patients the triceps skinfold thickness was measured with a Harpenden caliper The measurements obtained were compared to standards recently published for normal children and adolescents[10] With the use of these standards the skinfold thickness was found to be normal in 24 patients increased in 12 and decreased in three

Method of analysis All data were converted from analog to digital tape and interpreted for comparisons of pulse wave velocity indices, carotid and brachial pulse wave contours and systolic time intervals between diabetics and controls with the use of computer programs portions of which have been described.[11-13] The values of the measurements used for comparisons were the average of those calculated from all of the recordings on a subject.

Since the cardiac rates were significantly different (p<0 01) for the diabetic as compared to the normal subjects it was necessary to evaluate the effects of heart rate in the analysis Changes in systolic time intervals due to heart rate have been studied quantitatively and regression formulas have been used to correct for the effects of heart rate[14-17] The values for the systolic time intervals and the additional time intervals from the carotid and brachial pulse waves (see below) of the normal subjects were correlated with heart rate to determine which were dependent on rate changes Regression equations were obtained for these heart rate-dependent intervals utilizing the data obtained in the normal subjects These equations were then used to correct for the effects of heart rate by calculating the difference between the observed intervals and those predicted from the normal regression equations Pulse wave velocity however, does not seem to be

Table IV Systolic time intervals

Measurement	*Correlation with heart rate (normals)*	*Regression equation (HR) (normals)*	*Normals, mean ± S D (msec.)*	*Diabetics, mean ± S.D (msec.)*	*Difference of corrected means* (msec.)*	*t*	*p†*
Q-S_2	−0 83	483 9−1 46	374 2 ± 21 8	357 7 ± 27 1	−3 6	−0 99	NS
LVET	−0 87	385.5−1 35	283 6 ± 19 2	269 1 ± 23 4	−2 6	−0 86	NS
PEP	−0 16	–	91 9 ± 15 0	88 1 ± 18 1	−3 8	−0 89	NS
S_2 I	−0 08	–	31 0 ± 8.9	29 3 ± 7 6	−1 7	−0 82	NS
S_1-S_2	−0 86	432 3−1 55	315 2 ± 22 5	299 7 ± 26 1	−1 2	−0 41	NS
Q S_1	0 17	–	59 0 ± 10 2	57 8 ± 10 2	−1 2	−0 46	NS
ICT_2	−0 32	–	33 4 ± 11 8	30 5 ± 12 9	−2 9	−0 95	NS

*Same notat n s n first footnote to Table II
†Sam notat n s in second footn te to Table II

Table V Correlation between significant pulse wave abnormalities found in diabetic children and insulin dose

Pulse wave variable	*Correlation with insulin dose*	*p**
Brachial velocity	0 17	NS
Aortic velocity	0 08	NS
Brachial (I D)	0 51	p < 0 01
Carotid (I D)	0 44	p < 0 01

*The prob biliti s are gi en fo a two tailed test.

mal subjects indicating a greater number of diabetics than normals with a dampened dicrotic wave

In the carotid pulse wave (I D) also was significantly less for the diabetics (p<0 05) with a mean difference of 9 7 msec after correction for heart rate It is important to note that the parameter (I D) which was different between diabetics and normals is an indicator of arterial compliance [11] The direction in which both the carotid and brachial I D of the diabetics differed from normals indicates a decrease in compliance in the diabetic group

Systolic time intervals Several of the values for the systolic time intervals were significantly different between the two groups before correcting for heart rate (columns 4 and 5 of Table IV) However when the regression equations were used to correct for the difference in cardiac rate all variations in parameters for the two groups became insignificant. It is therefore reasonable to conclude that there were no differences in systolic time intervals between the diabetic and normal subjects that could not be explained by variations in heart rate

Correlation between pulse wave abnormalities and carbohydrate intolerance There was no correlation between the pulse wave velocities in the diabetic children and the degree of carbohydrate intolerance as indicated by insulin requirement (Table V) There was a correlation between the latter and pulse wave (I D) but it was the reverse of that expected, the greater the abnormal shortening of (I D) the *lower* the insulin dose and vice versa

Discussion

Dolger[19] was the first to point out in 1948 that vascular changes may precede by many years the appearance of hyperglycemia in patients with diabetes mellitus Siperstein and associates[20] found thickening of the basement membrane of muscle capillaries in half of the prediabetic subjects he examined. Camerini Davalos and colleagues[21] detected changes in the shape of the pulse wave in the digital arteries (increase in I/D ratio) in more than 50 per cent of prediabetic subjects The importance of the small vessels in the pathogenesis of diabetic peripheral vascular disease has been questioned by Strandness and his associates [22] who were unable to identify a specific lesion of small vessels in the lower extremities In every case the ischemic disease was explained pathologically on the basis of arteriosclerotic obstruction of major arteries Katz and his associates [7] while identifying an increase in pulse wave velocity in diabetic children did

Table II Brachial and carotid pulse wave time interval measurements

Measurement	Correlation with heart rate (normals)	Regression equation (HR) (normals)	Normals mean ± S.D (msec)	Diabetics mean ± S.D (msec)	Difference of corrected means* (msec)	t	p†
Brachial artery							
I D	−0 36	141 1−0 54	93 3 ± 19 4	80 9 ± 23 9	−14 6	−2 68	‹0 005
F I	−0 69	369 4−1 01	291 1 ± 19 0	290 5 ± 24 6	+6 5	1 57	NS
F P	−0 13	—	76 9 ± 13 7	79 8 ± 20 9	+2 9	0 63	NS
P I	−0 55	291 1−1 00	214 0 ± 23 5	210 8 ± 24 7	+3 8	0 70	NS
Carotid artery							
I D	−0 58	171 5−0 90	102 9 ± 19 7	85 5 ± 25 7	−9 7	−1 91	‹0 05
F I	−0 87	385 5−1 35	283 6 ± 19 2	269 1 ± 23 4	−2 6	−0 86	NS
F P	−0 46	139 2−0 49	102 1 ± 13 4	94 2 ± 21 2	−3 6	−0 80	NS
P I	−0 49	233 6−0 71	179 6 ± 18 3	173 9 ± 26 5	0 3	0 06	NS

*Represents the difference between the diabetic and normal measurements after making the appropriate correction for heart rate using the regression equations given in column 3

†The probabilities are given for a one tailed test of the difference between the time intervals corrected for heart rate

Table III Brachial and carotid pulse wave amplitude measurements

Measurement	Normals mean ± S D	Diabetics mean ± S.D	Difference of means	t	p*
Brachial artery					
I/D	0 50 ± 0 18	0 58 ± 0 24	+0 08	1 54	NS
I/P	0 23 ± 0 10	0 27 ± 0 16	+0 04	1 00	NS
Carotid artery					
I/D	0 80 ± 0 12	0 84 ± 0 19	+0 04	0 82	NS
I/P	0 40 ± 0 10	0 39 ± 0 15	−0 01	−0 22	NS

*The probabilities are given for a one tailed test.

Results

Pulse wave velocity indices The pulse wave velocity indices for diabetics and normals expressed as meters per second with standard deviations are given in Table I Both the brachial and aortic velocities were significantly greater in diabetics than normals with p values of ‹ 0 025 and ‹0 005, respectively

Pulse wave contours The results obtained from the measurements of the brachial and carotid pulse wave contours are presented in Tables II and III The correlations of the time intervals with heart rate for the normal children are included in Table II and normal regression equations as a function of heart rate are presented for the intervals significantly dependent on heart rate The mean and standard deviation columns contain data before correcting for heart rate The 'difference of corrected means' column represents the differences between the diabetic and normal measurements after making the appropriate correction for heart rate using the regression equations derived from the normal group

In the brachial pulse wave (I D) was significantly different between the diabetics and normals (Table II and Fig 2) After correction for heart rate the mean (I D) value for the diabetics was 14 6 msec less than normal (p ‹ 0 005) I/D in the brachial pulse wave was greater in the diabetics than in the normals. Although this difference was not statistically significant, 23 per cent of the diabetic patients had I/D ratios greater than 0 81 in contrast to none in the nor

parents It would appear from the present data that even the largest arteries including the aorta are involved. That the change could not be ascribed to an increase in ejection velocity is indicated by the failure to find an increase in myocardial contractility in the diabetic patients as judged by systolic time intervals

Huston and Abboud[25] used still another method for detecting loss of arterial wall distensibility in diabetic patients They calculated the ratio of the fall in pulse pressure to the fall in diastolic pressure after the inhalation of amyl nitrite Over half of the diabetic patients exhibited increased arterial rigidity by this index.

These various studies including the present report indicate that it is possible to detect large artery disease in diabetes using simple noninvasive procedures Such techniques should be applicable to the study of atherosclerosis in the general population to demonstrate the process in its early stages and to assess the effects of treatment. The predictive value of these methods must first be established by follow up studies in large population groups Since programs are now available fully automating the measurements[12,13] the time would appear to be at hand for their broad scale application

Summary

Arterial pulse wave velocities pulse wave contours and systolic time intervals were recorded in thirty nine diabetic children and were compared with recordings taken in twenty seven normal children Systolic time intervals were similar in the two groups of subjects However brachial and aortic pulse wave velocities were significantly greater in the diabetic than in the normal children ($p < 0.025$ and < 0.005 respectively) Also in the diabetic children the time interval from the incisura to the midpoint of the dicrotic wave (I D) was significantly shortened in both the brachial ($p < 0.005$) and carotid ($p < 0.05$) pulse waves as compared to the normal children These changes in pulse wave velocity and contour are associated with increased wall stiffness that occurs with aging and suggest that the large arteries of diabetic children may exhibit acceleration of the aging process The severity of these changes bore no direct correlation with the degree of carbohydrate intolerance as judged by insulin requirement.

The authors wish to thank Hubert V Pipberger M D for his collaboration in the use of computer facilities

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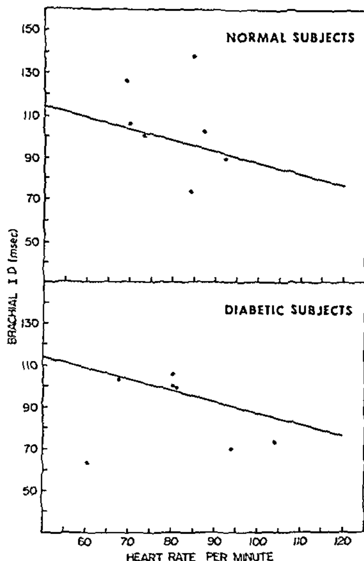


Fig 2 Values of (I D) plotted against heart for normal subjects (above) and the diabetic patients (below) The regression line of (I D) on heart rate for the normal subjects is drawn on both figures. Values for diabetic patients tend to fall below this line

not find any microangiopathy in ear lobes and gingival biopsies

Feinberg and Lax[23] could find no correlation between the severity of the diabetes as measured by insulin requirements and the frequency of abnormal digital arterial pulse wave contours, indicating the relative independence of the carbohydrate and vascular abnormalities of diabetes It thus appears that diabetes is a multisystem disease and that vascular changes especially in large arteries, may precede by years the appearance of carbohydrate intolerance The present series of juvenile diabetic patients also exhibited no positive correlation between the degree of severity of their carbohydrate intolerance as judged by insulin requirement and the extent of the arterial abnormalities Indeed, it would appear that while the two processes are frequently associated each can progress independently from the others.

The present studies confirm and extend the previously demonstrated arterial abnormality in diabetic children Our studies demonstrate that the larger arteries also show the same abnormalities of pulse wave shape found in the digital arteries by prior investigators [21-23] These changes consisted of a shortening and dampening of the dicrotic wave—reduced (I D) and increased (I/D) Furthermore, we had previously shown that similar changes in the carotid and brachial arteries are associated with aging and are a reflection of loss of vessel wall distensibility [11,24] The digital arteries are unusually responsive to temperature changes, emotion, and other vasoconstrictor influences which would influence the shape of the pulse wave irrespective of structural changes

To determine whether the brachial pulse wave I D would change with vasoconstriction in the skin three normal subjects were exposed to cold. The brachial pulse wave was recorded first at normal room temperatures of 72° F and again after 30 to 40 minutes of exposure in a cold room at 40° F Despite the development of marked coldness of the hands in all subjects there was no shortening of I D as compared to the recording taken at 72° F indicating that brachial I D is not affected by vasoconstriction in the skin The fact that the carotid artery showed similar shortening of I D makes it seem additionally unlikely that vasomotor changes in the skin could account for the observed changes

The possibility also was considered that the thickness of the skin overlying the brachial artery might influence the shape of the pulse wave and so change I D However there was no correlation between skinfold thickness and shortening of I D Of the 20 diabetic patients with the lowest values of I D 14 had normal triceps skinfold thickness as measured with the Harpenden caliper four had increased thickness and two had decreased thickness Therefore increased skinfold thickness could not account for the observed shortening of brachial I D

The present studies also confirm the observations of Woolam [3] Gunn [6] and Katz[7] and their associates that pulse wave velocity is increased in diabetic children or the children of diabetic

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Diazoxide – an effective vasodilator in accelerated hypertension

Marvin Moser M D *
White Plains N Y

Ample proof exists that the immediate treatment of accelerated hypertension has been lifesaving and is more than just an academic exercise Numerous studies including our own data have demonstrated that adequate blood pressure lowering in patients with malignant hypertension will frequently result in a reversal of a rapidly progressive downhill course [1-] This is true even in patients with evidence of renal insufficiency prior to treatment In these cases a temporary decrease in renal function usually occurs as blood pressure is lowered. Renal plasma flow and glomerular filtration rate will usually return to pre treatment levels however with stabilization of blood pressure and patients may live for many years if adequate blood pressure control is maintained. The syndrome of accelerated hypertension has become less common in recent years presumably because more patients are treated for elevated blood pressure at an earlier stage of the disease

In past years many different medications have been used in the treatment of malignant hypertension in an attempt to reverse both the pathologic process of necrotizing arteriolitis and the clinical syndrome of encephalopathy with or without congestive heart failure markedly elevated blood pressure and widespread vascular hemorrhages In the 1940 s tetraethylammonium chloride (TEAC) a ganglion blocking agent, and the veratrum derivatives drugs which interfere with baroreceptor and cardiac reflexes were used for emergency treatment. The duration of action of TEAC was extremely short and careful titration of the dosage was necessary The drug was not universally effective The veratrum drugs were potent but had a narrow range of safety and produced good results in only a limited number of cases. Blood pressure lowering was frequently followed by collapse nausea vomiting and other serious reactions.

In the 1950 s Hexamethonium another ganglion blocker was used both intravenously and intramuscularly with some success but responses were erratic and reactions frequent. Many patients did however experience a remission of the accelerated phase of hypertension with this medication Intravenous or intramuscular hydralazine (Apresoline) also proved to be effective in some cases of accelerated hypertension and is still being used for therapy especially in patients with acute glomerulonephritis or pre eclampsia

In recent years the treatments of choice have included (Table I) (1) Intravenous trimethaphan (Arfonad) a short acting potent ganglion blocking agent which must be monitored carefully Blood pressure rises rapidly after the infusion is stopped. (2) Intramuscular reserpine in dosages of 0 25 to as high as 5 0 mg every 4 to 6 hours This drug is effective in many cases (3) Intravenous pentolinium (Ansolysen) a longer acting ganglion blocking agent and less frequently (4) Oral mecamylamine (Inversine) Parenteral guanethidine (Ismelin) or alpha methyl dopa (Aldomet) have also been used with some success but have limited usefulness because of delay in response and a lower rate of effectiveness

Intravenous furosemide (Lasix) or the use of oral thiazide diuretics have proved of great value when used in conjunction with any of these drugs.

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Pharmacologic actions of diazoxide

Animal data have demonstrated that the blood pressure lowering effects of diazoxide probably result from a direct action on the smooth muscle tissues of the arterioles Unlike the ganglion blocking drugs, such as pentolinium diazoxide has little if any effect upon the tone of venous smooth muscle Venous pooling with a subsequent decrease in venous return and cardiac output do not, therefore occur The exact mode of action on arteriolar smooth muscle has not been determined. Several possibilities have been suggested.

1 The possibility that diazoxide produced a reduction of arteriolar tone by a direct stimulating effect on beta adrenergic receptors was investigated by injecting the drug into animals before and after the administration of propranolol a beta adrenergic blocking agent. These studies demonstrated that, while the heart rate and cardiac output increases normally seen after diazoxide were blocked by the propranolol injection blood pressure fell significantly Presumably therefore diazoxide reduces blood pressure by a mechanism other than stimulation of beta adrenergic receptors in the peripheral vessels [5]

2 The possibility that diazoxide has some primary influence on nerve pathways or humoral factors in producing its hypotensive effect has largely been ruled out by animal studies which have demonstrated that the blood pressure lowering effect of diazoxide is not blocked by previous administration of atropine phentolamine ganglion blockers such as hexamethonium antihistamines reserpine or surgical transection of the spinal cord [5]

3 There are some data to suggest that the effect of diazoxide on peripheral arteriolar tone is involved in some way with the interaction of the drug with calcium at the receptor site but an exact mechanism has not been defined

Approximately 90 per cent of diazoxide is rapidly bound to plasma protein in humans following an intravenous injection. Because of this the dosage must be given rapidly in a bolus to obtain the desired hypotensive effect.

Mroczek and co workers[6] have clearly demonstrated that when diazoxide is administered over a 10 to 15 second period of time rather than as a drip infusion or a slow injection a higher level or concentration of free (unbound) drug is available to be delivered to the arteriolar blood vessels and greater vasodilatation results This is especially true in accelerated hypertension where the initial degree of vasoconstriction is significantly greater than in less severe cases

Renal and cardiac actions

Although diazoxide has little direct effect upon the heart, cardiac stimulation results from a reflex response to arteriolar dilatation and the subsequent decrease in peripheral vascular resistance Increases in cardiac index from 50 to as high as 75 per cent and increases in heart rate of from 20 to 30 per cent have occurred within 5 to 30 minutes after a standard rapid injection of 300 mg of diazoxide intravenously in man [7,8] These changes usually occur simultaneously with a marked reduction of blood pressure an increase in pulse pressure and a decrease in systemic vascular resistance and left ventricular end diastolic pressure In many cases an acute blood pressure drop will occur in from 2 to 5 minutes after injection

The mechanism of diazoxide's antidiuretic and antinaturetic actions have not been clearly defined. In some animal studies, little effect on glomerular filtration rate has been demonstrated In humans, some investigators have noted an initial decrease in both renal blood flow and glomerular filtration rate renal function parameters return to normal in many instances within 1 to 2 hours Other investigators have noted a persistent decrease in renal blood flow which they attribute to a *secondary effect of* lowered blood pressure Antinaturetic effect probably results from enhanced proximal tubular reabsorption of sodium and a decreased delivery of salt and water to the distal portion of the nephron This may represent an attempt on the part of the kidney to conserve sodium and water as a result of blood pressure lowering and peripheral vasodilatation

Effect on blood sugar Intravenous diazoxide causes transient hyperglycemia and the chronic oral administration of the drug may result in more sustained rises in blood sugar Studies have indicated that the drug reacts both at pancreatic and extrapancreatic levels Diazoxide inhibits insulin secretion however in de pancreatized dogs the already high blood sugar levels increase further following an injection of the drug sug

Table I Effective drugs in "accelerated hypertension"

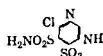
Drug	*Mode of action*	*Dosage*	*Disadvantages*	*Comments*
Reserpine	Catechol depletion Central effect	0 25 5 0 mg I M g 4 6 hrs	Delay in B P response (1 2 hours) Excessive drowsiness. Effect not always predictable	Effective in many cases. Should not be used for longer than 24 48 hrs.
Trimethaphan (Arfonad)	Ganglion blocker	I V dosage titrated by B P response (1000 mg /L)	Hypotension Short duration of action constant moni toring necessary Excessive B P fall Dosage variable	Effective in many cases Prolonged use impractical
Pentolinium (Ansolysen)	Ganglion blocker	I M or I V (1 0 mg −20 mg) must be titrated	Excessive B P fall Dosage variable	Longer duration of action (4 12 hours) An advantage over shorter acting drugs.
Hydralazine (Apresoline)	Vasodilator	15 30 mg I M or I V	Effect unpredictable Excessive tachycardia	Low rate of response Most effective in acute nephritis and severe toxemia of pregnancy
Nitroprusside	Vasodilator	I V Dosage Variable Titrate by B P response (100 mg /L)	Short duration of action Constant monitoring necessary Unstable solution	Not generally available
Diazoxide (Hyperstat)	Vasodilator	300 500 mg I V (as a bolus)	Transient hyperglycemia Nausea	Rapid effect 1 5 min.—high rate of response (over 75 percent) Standard dose Relatively long duration of effect 2 12 hours

The above drugs produce a fall in blood pressure in many cases and their use frequently results in an excellent long range response How ever many have side effects for example ex cessive sedation and even coma following in creasing doses of reserpine and excessive blood pressure fall from intravenous ganglion blocking agents such as pentolinium lack of response in many patients after intravenous hydralazine or the inconvenience of constant monitoring and possible danger from the administration of in travenous trimethaphan These problems have led to a continuing search for a more reliable effective treatment of accelerated hypertension

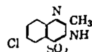
Intravenous sodium nitroprusside is an effec tive vasodilator and has been used successfully by several investigators[3] This drug must be pre pared just prior to use and is unstable in solution It is not available in most institutions but, when a stable preparation is released for use nitro prusside may become one of the preferred treat ments of accelerated hypertension Unfor tunately, the blood pressure lowering effects of the drug are of short duration and constant monitoring of a continuous intravenous infusion is required.

The recent introduction of *diazoxide* (Hy perstat) for intravenous use in accelerated hy pertension represents a major breakthrough in treatment

Diazoxide is a non diuretic agent related to the benzothiadiazines Unlike chlorothiazide which it resembles structurally diazoxide administra tion results in sodium and water retention yet blood pressure is significantly reduced.



Chlorothiazide



Diazoxide

Summary

1 *Diazoxide* is a potent arteriolar vasodilator which when administered rapidly (within 10 to 15 seconds) by the intravenous route lowers recumbent blood pressure significantly without producing postural hypotension in a large percentage of patients with accelerated hypertension Antihypertensive effect occurs within 1 to 5 minutes and persists for from 1 to as long as 18 hours Cardiac output is increased.

2 The ease of administration (a single bolus), relatively long duration of action lack of significant acute side effects and a high rate of response even among patients with renal insufficiency make diazoxide a preferred drug for the emergency management of accelerated hypertension

3 Repeated injections may result in diminished effectiveness, sodium retention, and hyperglycemia The concurrent administration of furosemide is frequently necessary therefore to produce a continuing antihypertensive effect

4 Patients should be placed on oral antihypertensive therapy with other drugs as soon as the clinical condition is stable

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gesting an extra pancreatic effect The hyperglycemic effect of diazoxide is eliminated in adenalectomized and pancreatectomized animals Diazoxide causes a direct increase in catecholamine levels which decrease insulin release This action may explain at least a portion of the effect on blood sugar

Glucose levels in animals have generally returned to normal within 24 hours after the drug is stopped and studies have failed to demonstrate significant long term effects on blood chemistries, or electrolyte values

Method of use in accelerated hypertension Diazoxide is supplied in 20 c.c ampules containing 300 mg of the drug Because the solution is alkaline it is important to avoid extravasation of the fluid when a rapid intravenous injection is given If some fluid does leak into the tissues, severe burning sensation and pain may occur and persist for 2 to 3 hours The injection of the bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases [9] A maximal blood pressure response usually occurs within 5 to 10 minutes We have noted a rapid return in blood pressure in some patients within a 15 to 30 minute period of time (usually not to pretreatment levels) in other cases a rise in pressure is noted within 1 to 2 hours and the drug may have to be given again In most instances, however blood pressure lowering persists for from 6 to 18 hours As noted above a slower injection will frequently be ineffective Diazoxide may be administered every four to six hours in an effort to "titrate" the blood pressure to levels where symptoms and signs of accelerated hypertension will begin to clear

$$150/90 - \frac{160 - 170}{100} \text{ mm/Hg}$$

Blood pressure reduction occurs in the recumbent position and only a slight additional postural fall in blood pressure is noted following the injection of diazoxide This is in marked contrast to results obtained with the ganglion blockers (pentolinium or trimethaphan)

Side effects

Symptoms suggestive of a decrease in coronary or cerebral blood flow may occur but are uncommon, despite the rapid fall in blood pressure and the often critical condition of the patient Some instances of non specific electrocardiographic changes have been reported following intravenous administration of diazoxide [11] If an "overshoot or marked hypotension does occur, it can be counteracted by the Trendelenburg position or by the administration of sympathomimetic drugs

Repeated injections of diazoxide may cause increasing sodium retention decreased urinary output, and congestive heart failure A decreasing effect on blood pressure with successive doses may also occur For this reason the simultaneous administration of a potent diuretic agent such as furosemide is indicated in most cases [10] Forty to 120 mg should be given immediately and repeated every 8 to 12 hours as necessary to maintain an adequate urinary output (1 5 to 2 liters daily) In patients who are nauseated or comatose intravenous administration is necessary In others furosemide or a thiazide diuretic may be given by mouth Our experience has indicated that in patients with poor renal function large doses of furosemide may be necessary (120 to 160 mg every 4 to 6 hours for 1 to 2 days)

Repeated injections of diazoxide increase the risk of hyperglycemia Finnerty[6] suggests concomitant treatment with oral antidiabetic drugs when possible in patients with known glucose intolerance In diabetics receiving more than 1 to 2 injections of diazoxide additional insulin will usually be effective in reducing blood sugar levels Hyperglycemia following one injection of diazoxide is usually transient and persists for only 12 to 18 hours

It is important to wean the patient away from parenteral therapy as soon as possible This usually can be done within 1 to 2 days or after 2 to 3 doses of diazoxide and a potent diuretic agent. Blood pressures can usually be brought under control and symptoms of encephalopathy reversed unless the patient has severe azotemia The use of oral thiazides and one or more of the other antihypertensive drugs (Rauwolfia, hydralazine, methyldopa propranolol or guanethidine) should be instituted as soon as oral therapy is tolerated

Diazoxide is ineffective in treating blood pressure elevations secondary to pheochromocytoma

Acute reactions Following the injection of diazoxide, flushing some abdominal discomfort, nausea sensations of warmth, and occasional throbbing headache and sweating may occur These reactions usually are of short duration

Summary

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Annotations

The cause of arterial disease

Sir William Osler did not mention heart attacks in his 1910 lectures. The first clinical description of the coronary heart attack was made in 1912.

Angina pectoris was first described in 1768. From that date and until the second or third decade of this century it was extremely rare and was caused by syphilitic heart disease and gross anemia.

Dr Paul Dudley White, President Eisenhower's physician at the time of his heart attacks, did not see his first case until 1920. Since 1956 heart attacks have become more common, so that in the U.S.A. 500 000 people die from this condition every year.

It appears therefore that atherosclerosis is a disease of this century with a characteristic 20 year time lag. Something was introduced to the diet of those people affected which brought about the pathological change, and this substance, whatever it was, was taken in still greater quantities after the middle fifties.

Atherosclerosis is confined to Western countries. The only exceptions to this rule are individuals and communities in Western countries who by chance or deliberate choice have been able to avoid the health hazards of a Western diet, and individual groups and communities in non Western countries who have been subjected to a Western diet. Of all the European countries France has the lowest incidence of degenerative heart disease (90 deaths per 100 000 population per year), only one half of the next lowest (Netherlands, 190 deaths per 100 000 population per year) and only about one fourth of the highest (Sweden, 360 deaths per 100 000 population per year).

There are 700 000 000 people in China. Heart attacks are virtually unknown. The poor are vegetarian. The more well to do eat food with a high fat content. The water is foul and gastrointestinal infection and infestation are widespread—but there are no heart attacks.

During two years work on a one man bush station in the Congo from 1963 to 1965, looking after 80 000 patients (and sometimes the whole province when my two colleagues were on leave) I never saw a single case of heart attack. Lest anyone should argue that the average age of death there is very low, which is true, I would state that it is common for people, men and women, to live beyond 70 years once they have survived the debilitating tropical diseases which take many more before the age of 50. I would also state that these old people were hale and hearty, not sitting huddled over a fire awaiting the grave in a cabbage condition.

One researcher, when I said "Show me one community drinking chlorinated water where the incidence of atheroma is low", quoted Aden, where the water is highly chlorinated. My answer to this one is: "Go to Aden and you will find that the indigenous inhabitants use their ancient wells, the expatriate men drink beer and other alcoholic beverages at the club (and refuse chlorinated water in their Scotch) and the women do likewise in the evening but drink boiled water in their coffee and tea in the morning and afternoon. Boiling drives off the chlorine. Even supposing a teetotaller gets the chlorinated water, his short tour of duty is insufficient to affect his arteries."

Every American knows the custom in U.S. bars where the barman puts down a glass of water and then says "What will I get you, sir?" More than likely he will reply "Scotch on the rocks." So he gets a fair dose of chlorinated and softened water.

There is a community of Italian descent at Roseto in Pennsylvania among whom heart attacks are unknown. They eat a highly saturated fat diet but drink water from mountain springs. Members of the community who have left Roseto for an urban life have been traced subsequently and were found to have died of heart attacks.

In a little bistro in Les Marecottes in the Canton du Valais in Switzerland there is to be found on the wall a cardboard plaque printed in gold letters, as follows: *Avis a tout le monde*. Age moyen de mourir: Buveurs d'eau 55 ans. Buveurs de vin 70 ans. A vous de choisir. (*Translation*: "Take notice, everyone, of the average age at death. Drinkers of water die at age 55. Drinkers of wine die at age 70. Take your pick.") A search through all the literature on atherosclerosis fails to find one worker who has incriminated alcohol as a cause.

Cleave and Campbell[1] have shown quite conclusively that coronary disease in primitive communities in Africa and India is confined to those living in urban areas under Western conditions. I would be the first to agree with them that the diet of Westernized, protein stripped carbohydrate and sugar of these communities is a cause of this high incidence of coronary disease, especially since the change of the improver of white flour from Agene to chlorine dioxide in the middle fifties. At the same time it is true that chlorinated water is exactly correlated geographically with a Western diet.

Pre menopausal women get atheroma, but with less frequency than men of comparable age. After the menopause this gap is gradually closed. They drink tea and coffee.

G.I.s in the Korean war of average age 22.1 years killed in battle were found at autopsy to have advanced atheroma in over 75 per cent of cases. Medical officers of the South Korean detachments were emphatic that atheroma among Koreans is unknown. Their water was from natural sources. The water given to American troops was so heavily chlorinated that it was virtually undrinkable. This same phenomenon was observed personally by Dr Joseph M. Price[2] when in Vietnam, and the incidence of atheroma there among young battle casualties was even higher than in Korea.

When water chlorinated to a level not much higher than in Korea and Vietnam is given to roosters, along with chlorinated mash, they fall ill within 3 weeks and die within 3 months. At autopsy gross lesions of atheroma are found. A control group of roosters given distilled water and untreated mash remained healthy. The spontaneous lesions of

atheroma reported in chickens is found only in those given chlorinated water "Spontaneous" atheroma reported in captive animals occurs only in those drinking chlorinated water

The experiment on roosters described above was suggested to Dr Price[2] when he was a medical student and saw the "milkstone" on the inside of the metal and rubber tubes in the milking machine on his father's farm He discovered that this occurred only when the sanitizer used to cleanse the apparatus contained chlorine This impression was reinforced when he saw the atheroma present on the inner surface of synthetic vascular grafts (artificial Dacron) removed at autopsy from patients operated on some time before for arterial disease This suggests that there is some validity in the "encrustation" theory of plaque formation, but does not preclude the possibility of damage to the arterial wall causing edema and necrosis in the microcirculation and making the intima therefore susceptible to lipid deposition. If such can be a possibility damage to the microcirculation could occur in other areas and be responsible for example for the symptoms of cerebrovascular degeneration by reinforcing the effect of the cerebral ischemia due to atheroma of the large arteries supplying the brain.

If during the last decade of the nineties, when the use of chlorination was started, the authorities had known of modern alternative methods such as ultraviolet irradiation or ozonation atherosclerosis would not have arisen Yet chlorination is still the sacred cow of public health authorities

There are four main ways in which our food has been modified since 1900 (1) Wheat and other grains have been robbed of the germ and outer layers, which have been given to pigs and cattle (2) The consumption of sugar in Western countries has risen to over 112 lbs. per head per annum (3) Chlorine has been added to water and since 1956 to white flour The water is often artifically softened and (4) Hundreds of substances are used in food as colorings, flavorings preservatives sweeteners emulsifiers, softeners antioxidants, bleachers. Very little is known about most of these, and as in the case of chlorine in water and flour they are used indiscriminately until proved toxic

This vast experiment in nutrition, promoted for the convenience and profit of the commercial interests involved has been bypassed by an ever increasing number of people labelled as cranks, who follow a reform diet of whole grain products no white sugar fresh salads vegetables and fruit eggs, and butter and nuts, and sometimes flesh foods They know all about vitamins, trace elements and enzymes and a good deal about poisonous additives They constitute a useful control group and work is proceeding to ascertain the incidence of ischemic heart disease in this group as well as all the other conditions known to have arisen as a result of a Western diet Sufficient is already known from this investigation to suggest that a return to a reform diet is the only way to prevent these diseases and in some cases—e g peptic ulcer cure them

In the use of this knowledge it is not sufficient to pick out one factor affecting a given disease such as the chromium in wheat grains which is found to be deficient in the tissues of people dying of heart attacks, and put just that one thing right. Whole wheat is the most complicated food known. Besides chromium it contains at least twelve further metals, and at least seven vitamins The effects of the deficiency of most of these is known, but what we can be sure of is that as a matter of evolutionary development, man needs whole grain. Of course known poisons such as chloride dioxide should be forbidden by law

Enough has been written by Professor Yudkin[3] on the role of sugar in disease to establish the truth of his description of this ubiquitous food constituent as a killer Caries of the teeth childhood obesity increasing children's susceptibility to infection obesity peptic ulcer constipation varicose veins, and last but not least coliform infections and cardiovascular disease all come under this heading

Much has been written about the role of cholesterol There is no such thing as a normal blood level What is normal for one person is abnormal for another An eskimo eating several pounds of blubber at a sitting but drinking melted snow can support throughout life a level far above what Western cardiologists would call normal without incurring the risk of arterial disease So also for a fat Chinese or an inhabitant of Roseto This does not mean that as an immediate measure for someone already at risk the doctor should not try to reduce the level But in addition, he should remove the cause by advising unchlorinated water and whole grain flour products since in the presence of chlorine there will be enough cholesterol around even when he has reduced the level to provide the deposition of lipids There is no more reason to lower cholesterol levels while the chlorine remains operative than there is to neutralize the hydrochloric acid in the stomach in a case of peptic ulcer while the diet remains predominently protein stripped carbohydrate and sugar However it is worth repeating that people on a reform diet consistently have a low cholesterol level

Another example in discussing diet and disease of the necessity to avoid singling out one thing at a time and putting this right is the clear injunction to take plenty of fresh vegetables salads and fruits. There is more to this than the cure of constipation and the avoidance of scurvy which most doctors regard as the only condition caused by vitamin C lack. There is evidence from Spittle[4] that vitamin C has a part in the cholesterol regulating mechanism of the body She even goes so far as to say "Atherosclerosis is a long term deficiency of Vitamin C This statement gave rise to a long cross discussion by letter in the LANCET while at the same time ascorbic acid was implicated in the prevention of the common cold[5] and in the suppression of cell proliferation and cancer[6] The implications for the man in the street and for doctors not involved in becoming more and more expert in one tiny field of research are clear These constituents of natural foods are not in the same category as drugs which are foreign to the body and are given for a specific effect They are part of man's evolutionary heritage and most of his illnesses are due to his being deprived of them And the man in the street and the doctor who treats him cannot afford to wait until the researchers climb out severally from their expertly dug holes and get together around a computer to give their final grand solution. Ordinary people will recognize the simple logic of my thesis Our Western diet is an experiment in man made evolution which should never have been attempted and which should be reversed

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Blumberg's Australian antigen

This communication summarizes some of the recent data published relative to Blumberg s Australian antigen. The antigen was found by him in a high frequency in the serum of patients with hemophilia and in those patients who had received multiple blood transfusions Of interest is that Blumberg after studying several thousand sera found it only in 0 1 per cent of Americans but it was common in persons living in Asia and tropical countries. An early work of significance was that of Okochi and Murakami[1] describing anti HAA and its association with hepatitis. Community family epidemiological studies have shown that family clustering of HAA occurs.[2] Sex distribution studies have demonstrated the frequency of the Australian antigen to be greater in males than in females. In a recent report by Ulstrup and Figenschow [3] the highest percentage of positive individuals with Australian antigen was in the 38 to 42 year age group

In a study by Dodd and associates,[5] they found that the population centers with an incidence significantly lower than the national average of 0 14 per cent were almost always in the Northeastern states whereas the centers with significantly higher incidence were from the Southeastern states or from large urban areas It was their opinion that it was not clear whether this variation in incidence was due to differences in population density and over all living conditions or to a geographic variation in the socioeconomic structure of the volunteer donor population or to other factors A review[6] has been published on the acquisition of antibody to hepatitis B antigen in three socioeconomically different medical populations The frequency of antibody to hepatitis B antigen was in general related to the age and inversely related to the socioeconomic status of the individual Little antibody was acquired before 20 years of age but between 20 and 50 years of age there was a striking rise with no significant increase thereafter In the lowest socioeconomic group 43 per cent of patients by age 50 had antibodies present while in the highest economic group their level was only 15 per cent by age 50 It was the conclusion of the authors that certain populations especially those of low socioeconomic status seemed to be saturated with hepatitis B virus They further concluded that the high rate of hepatitis B virus detected probably meant that the reservoir of hepatitis B in the general population was far larger and that the resultant public health problem far greater than previously thought

Incidence studies of the Australian antigen on 2 400 asymptomatic blood donors performed at this hospital in 1971 revealed an incidence of 0 4 per cent positives Blood donors studied in 1972 5 615 in number revealed 0 17 per cent positives. The technique used was Spectra s Counter Electrophoresis. Sera from 977 blood donors in 1972 were studied by both counter electrophoresis and radioimmune assay technique Seven positive sera were detected by radioimmune assay and none by counter electrophoresis. The radioimmune positive sera were repeated again by counter electrophoresis and in all instances the sera were again negative [4] As a result of this data all blood donors are now screened by radioimmune assay for the Hepatitis Associated Antigen. Of major concern is that units are now tied up in excess of 18 hours. The incubation period is 16 hours for the RIA procedure Previously when units were checked by counter electrophoresis, the processing period was approximately 2 hours. Because of the long delay associated with radioimmune assay we have had to retain counter electrophoresis capabilities to process those units of blood needed for platelets, etc

The Hepatitis Associated Antigen was originally described as a single antigen by Blumberg and co workers. Data has been published recently that the antigen is heterogeneous,[7 9] and is made up of various antigenic determinants Three determinants have been described *a*, *d*, and *y* Determinant *a* is common to all HAA particles and the *d* and *y* determinants appear to be mutually exclusive These latter determinants appear to reflect the genotype of the virus. Kok Doorschodt and colleagues[9] have labeled two types of Hepatitis Associated Antigen and antibodies. AB and AC. These were demonstrated by immunodiffusion blocking of antigen with type specific antibodies and absorption of antibodies by saturation with heterotyping antigens It was concluded that both determinants were carried on one particle and it was suggested that these two types of HAA could be separate infecting agents Holland and co workers[10] suggest that the subtypes of HAA appear to be determined by the viral agent and not by the host and that they remain the same (subtype) in the effected individual The frequency of both *ad* and *ay* subtypes are about the same for patients with active viral hepatitis The subtype *ad* is also found in patients with chronic hepatitis and is more commonly found in blood donor carriers than is *ay* Data have also been published that there is physiologic as well as immunologic evidence of the heterogenicity of HAA [11]

It is of importance to note that HAA testing is not only complicated by the heterogenicity of the antigen, but also by the variation in the relative concentration of antibodies against the known different HAA determinant. A postulate has been presented that the previous reports that HAA car

ners have higher titers of antigen than individuals with acute or chronic hepatitis may reflect subtype differences in antigen rather than actual differences in the total amount of antigen present[12]

Dudley Fox, and Sherlock[13] have submitted data on cellular immunity and HAA liver disease They present the hypothesis that hepatitis associated with HAA is not due to an immune complex disease but a disease resulting from a response controlled by T (thymus dependent) lymphocytes. It is to be noted that immune complexes of HAA and immunoglobulins have been reported in some HAA positive patients. These complexes have been reported as etiological agents in vasculitis[14] and in cases of nephritis.[15] Support for the data of Dudley and associates is given by the fact that HAA is frequently found in sera in individuals with no clinical or biochemical evidence of liver disease

Reviews on HAA hepatitis have commented upon the possible significance or role played by serum inhibitors on lymphocyte transformation This question may have importance with the data published by Dudley and co workers.[13] Brooks,[16] in commenting on this subject writes that the question of delayed hypersensitivity reactions (and HAA hepatitis) may be related to either persistent cellular defect or to the presence of a persistent serum inhibitor which starts lymphocyte transformation Recent data have suggested that the serum inhibitors of lymphocyte transformation may be a gamma globulin[17]

Popper and MacKay[18] have presented a hypothesis that the Australian antigen particle of Type B hepatitis represents an infectious agent different from viruses so far described The antigen is described as an RNA antigen complex with an amount of host protein far in excess of the protein of most other viruses Acute type B viral hepatitis is regarded as a restricted immunological response to the proteins in the complete B antigen particle The chronic liver disease associated with hepatitis associated antigen may be related to the following processes continued restricted immune reactions to the viron or more probably to the protein of the whole particle or persistent autoimmune reaction to specific host component of broken down B antigen particles in the absence of viron

Electron microscopic studies of the Australian antigen has demonstrated three forms They consist of circular particles and tubular forms which measure approximately 200 A in diameter and a larger double shield particle or Dane form[20] It has an outer diameter of 42 nm and an inner component with a diameter approximating 28 nm Ninety four per cent of 50 healthy blood donors, whose sera were positive for HAA were found to contain the Australian antigen by electron microscopic examination[19] Antigen particles vary considerably in these cases In 30 per cent of the donors, the Dane particle[20] was found, and in 50 per cent of the samples studied visible aggregates resembling antigen antibody complexes were found.

The dynamic status of Blumberg's Hepatitis Associated Antigen is soon realized by reviewing the quickly expanding publications covering this fascinating subject.

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The cruelties in the practice of medicine

In the attempt to relieve the *suffering* and to cure the sick, we usually forget the psyche The only thing that counts in life is *happiness! Good health, both* mental and physical is essential for happiness. Even though this is well accepted too frequently the psychic *state of* the patient is ignored, almost completely at times This is best exemplified with little children To little *children* hospitals are institutions of tor ture The present day hospital facilities *designed for the* care of children are archaic The construction hospital rules regulations and practices and the attitudes practices and behavior of the attendants (physicians included) are con cerned primarily with *getting a job done rapidly* efficiently and inexpensively But what about each little patient *whose life is* one of obeying satisfying and *pleasing elders? To roll* a nice little crying 5 *year old girl* in an iron crib with the sides elevated to produce an enclosure with vertical bars like *those of a prison merely for* an x ray or throat examination while the mother after kissing her is left behind on another *floor of the hospital* vividly displays the effects of psychic stress. This practice is not necessary! What harm to *hospital* policy and routine would ensue if the mother were allowed to accompany her little daughter to provide comfort and the necessary and tremendous psychic support on this journey *of horrors* Yes, a journey of horrors at the moment to the little delicate 5 year old girl The presence of the mother would greatly comfort not only the little girl but the mother too

And, why not insist that all hospital facilities always provide *proper facilities in the* same room for the accompanying mother as well as for the child? There should be comfortable beds *kitchenettes T V books etc* for the mother and her sick child I suppose the reason is only *money* Regardless of the reasons the present system is cruel And what are the *resultant effects of these* clinic and hospital experiences in the immediate and future life of the little girl? Sickness it self is cruel and painful—management should never be Treatment of the sick should always be designed *to produce* comfort to the patient and the relatives and much comfort can be provided *merely by* kindness, attention, and helpful ness *at all times Little children do* not understand *what is* happening To a child there is no solace as potent as the pres ence of a loving mother Hospitals must be designed *organized* and operated to make it possible for a mother to be with her sick child at all times.

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Selective coronary arteriography during permanent ventricular tachycardia

Left ventricular aneurysm develops as a complication of myocardial infarction in approximately 10 to 15 *per cent* of cases[1] In rare instances it may result in *recurrent* life threatening ventricular arrhythmias Surgical excision of the aneurysm with or without combined revascularization[1] has been reported to terminate the arrhythmia [2-6] We would like to report briefly the case of a patient *who underwent* uneventfully a selective coronary arteriography in spite of a *permanent* ventricular tachycardia due to a left *ventricular* aneurysm

A 62 year old patient was admitted to our *department on* October 18 1972 for the recent onset of multiple ventricular premature beats He had had an anteroseptal wall infarction in 1962 and had been free of any symptoms except for tran sient episodes of palpitations During the hospitalization course short runs of ventricular tachycardia occurred fre quently A few days later ventricular tachycardia became permanent at a mean rate of 150 beats per minute and per sisted for weeks (Fig 1) Antiarrhythmic agents cardiover sion, and atrial and ventricular pacing failed to terminate or to prevent the recurrence of the arrhythmia Surprisingly enough the patient remained almost asymptomatic Left ventricular aneurysm was suspected. Although ventricular tachycardia was permanent a percutaneous selective coro nary arteriography[7] was performed on November 17 1972 *after* a transvenous unipolar pacemaker was positioned in the right ventricle by way of the right femoral vein The pro cedure went uneventfully It showed a complete occlusion of the left anterior descending artery The right coronary artery *was* free of significant stenosis A left ventriculogram evi denced a large aneurysm of the anterior wall Surgical exci sion of the akinetic area was successfully performed on December 7 1972 without combined revascularization Thirteen months later the patient is doing well He is free of any arrhythmias

Preoperative cardiac catheterization and/or cineangiocar diography have been performed in a few cases with *recurrent* ventricular tachyarrhythmias due to ventricular aneurysm [3-6] However to our knowledge there has been no report of selective coronary arteriography during *permanent* stable ventricular tachycardia [8-10] This unusual observation brings an additional *proof that* percutaneous selective coro-

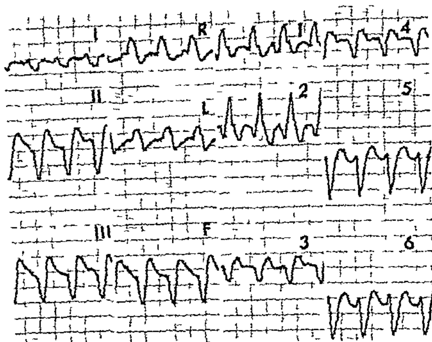


Fig 1 Electrocardiogram of 62 year-old man patient Ventricular tachycardia was permanent for weeks

nary arteriography may be a quite safe procedure in expert hands. If necessary it can be done in patients with severe ventricular arrhythmias

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Letters to the Editor

Potential toxicity of excessive polysaturates

To the Editor

The editorial in your June 1973 issue *(The potential toxicity of excessive polysaturates,* by E. R Pinckney) requires pointed comment Every physician is well aware that too much of any substance even water may become toxic However under the shield of a time honored maxim Do no harm " the author has advanced sketchy and largely unsubstantiated postulates to cloud the specific question of modify ing the usual American diet by increasing the intake of polysaturated fatty acids Critical partial review of the references supplied often reveals a lack of relation or no support for many of the sweeping inferences made

Consider the author s fear raising repeated[1] assertion, And there is certainly a reasonable epidemiologic association between a diet high in polysaturates and increased incidence of cancer (especially gastric) in humans. The word reasonable implies reasons presumably specified in the references listed to support the allegation Turning to these I find that the only one of the four which makes any mention of polyunsaturates is one by Pinckney himself protesting advice to use unsaturated vegetable oils in cooking lest it alter their character detrimentally Any deleterious change from average heating is denied by sound authority on the same page[2]

Indeed, evidence from the editorial itself is at odds with the claim of any epidemiologic association. How does the author reconcile his claim that the American intake of polyunsaturates has risen threefold in the last 50 years, the above quoted assertion and his own reference s statement[3] that the white population of the United States has the lowest incidence of cancer of the stomach in the world in recent decades?

Among his other references is one that is pertinent[4] of a clinical study in which an increased incidence of cancer was found in a group of 424 men who consumed a diet high in polysaturates as opposed to a group of controls over an eight year period. However Dr Pinkney fails to mention that Ederer and associates[5] in the same year incorporated these subjects with those of four other studies to triple the size of the experimental cohort and found that the differences in mortality rate vs the controls were not statistically significant They concluded that the evidence does not support the hypothesis that cholesterol lowering diets *are carcinogenic*

The editorials your journal publishes deserve as much scrutiny as the articles you accept. It is unfortunate to lend the prestige of your editorial page to create reservations among practicing physicians in the support of the critical current large scale trial of lipid diet therapy (plus blood pressure and smoking control) *This is the Multiple Risk Factor Intervention Trial* (MRFIT) for prevention of heart attack, funded by the National Heart and Lung Institute that is to function in 20 designated centers in the country for the next six years.

All resources of medicine should support this effort to find a pragmatic answer to one of the major health problems of this country the accelerating rate and earlier onset of coronary artery disease and myocardial infarction.

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Reply

To the Editor

Dr Baldwin s need to make pointed comment about the editorial in question is most appreciated for it serves to renew attention to the subject matter and to discuss the latest findings related to that editorial which was written more than two years ago However in twice expressing his personal fear that such an allegedly unscrutinized editorial will create reservations among physicians thereby causing them to fail to support certain diet heart studies such as those being conducted by Dr Baldwin (MRFIT) he misses the main idea of the editorial (as expressed in its subtitle) Do not let the patient harm himself — by ingesting an excessive amount of polyunsaturated fats.

This proposed point of view came about after personal study of patients who admittedly under the commercially created impression that certain margarines and oils would prevent or treat heart disease had surreptitiously increased their polyunsaturate intake by 300 to 400 per cent within a period of from one to 10 years. Only after salient questioning did those patients reveal such self imposed dietary eccentricities as directly swallowing 8 tablespoons of corn oil daily (after reading about this in a health column) using large amounts of corn oil on toast every morning eating nothing but fish and/or skinless poultry for protein etc In many instances the patients problems ultimately *seemed* related to their deliberately altered diet. The evident association between an *excessive* polyunsaturate intake and a host of adverse clinical conditions certainly justifies reporting this observation to the medical profession, and ample collaborative reports may be found in many of the 155 references supporting the paper cited (erroneously) by Dr Baldwin.[1] A

more recent finding[2] adds to this evidence indicating that a diet high in polyunsaturates can precipitate more than twice as much cholelithiasis as is found in those diets containing a fairly typical fatty acid distribution (control diet). Within the past year there has also been a report on a form of nutritional muscular dystrophy where dietary unsaturated fatty acids were deliberately used in increased amounts and were not protected by biologically effective antioxidants. Special attention was called to the failure of protecting polyunsaturates against peroxidation as a potential interference with myocardial metabolism which makes the heart more vulnerable to ischemia.[3]

But because Dr Baldwin stresses pointed comment it is only fair that all his points be answered. In his evident anger Dr Baldwin flagrantly contradicts himself when he wrongly makes the accusation that he finds only *one* reference to diet, polyunsaturates, and cancer in the editorial and then in his own two subsequent paragraphs pointedly cites two additional references to that same subject that were also part of the same editorial. Insofar as the Ederer paper is concerned, the incidence of cancer in those on a cholesterol lowering diet depends on how one wants to interpret the statistics offered. For in that same paper Ederer also reports on a study in Oslo where cancer cases were greatly increased in those eating a high polyunsaturate diet—confirming the now famous Pearce and Dayton study in Los Angeles. When all five studies in five different cities are combined (the essence of the Ederer paper) there is certainly enough reason to bring the matter to the attention of physicians. Of particular interest while quoting the Ederer paper's inference on the cancer polyunsaturate relationship Dr Baldwin fails to quote the other equally emphasized, published conclusion that "the life saving potential of serum cholesterol lowering diets is not proven."[4] In yet another fairly recent report on diet in relation to heart disease Bierenbaum and associates[5] stated "The degree of unsaturation of the fats in the experimental diet (high in polyunsaturates) did not appear to influence serum cholesterol value or mortality."

Additional data on the dietary fat–cancer relationship can be found in the work of Carroll and Khor.[6] As to Dr Baldwin's mention of the Ackerman article (his reference number 3) this excellent review of food and cancer was used to show the higher incidence of stomach cancer in countries that normally stress polyunsaturates in their diet. The Japanese who have the world's highest mortality rate from stomach cancer still eat more polyunsaturated than saturated fats.[7] The same report, incidentally attributed little importance to the increased intake of cholesterol and fats in general as a cause of the rising Japanese CHD rate. In the United States the reported threefold increase in polyunsaturate intake is a relatively recent innovation, and *excessive* polyunsaturate intake is still not a dietary common denominator. It could be years before we have sufficient clinical evidence of either harm or efficacy of any alteration in the fat content of our diet. In the meantime should not all of the possibilities be investigated rather than suppressed?

Next we come to Dr Baldwin's attempt to discredit the matter of deleterious effects when unsaturated fats and oils are heated. While this point was not even mentioned in the editorial, there still are many references to substantiate the fact that the particular fatty acids (e.g. linoleic acid) of a polyunsaturated fat link together (peroxidation) during heating and polymerize.[1,8] Polymerization lowers the iodine number of a fat which is the specific measure of the increased saturation of that fat. In a paper delivered to the American Heart Association in 1970 Dr Neal R. Artman,[9] of the Proctor & Gamble company has stated that when such fats are heated in air even at low temperatures, "linolenate is largely converted to polymers or varnish."

Many in the MRFIT and similar programs, especially Harvard's Department of Nutrition have already made public their intention to prove once and for all that dietary fat intake and CHD have a cause and effect relationship a rather dogmatic determination for a truly scientific trial that has just gotten under way.[10] Indeed, press releases from NIH, sponsor of these programs, already promote the success of such studies prior to their conclusion.[11] But such studies are really being conducted under what the 1973 President's Panel on Heart Disease calls more a "matter of faith than fact."[12] The various groups that endorse the *trial* of the lipid diet theory do not even suggest let alone recommend, that the general population alter its diet habits in regard to the nature of specific fats.[13,14]

In another recent study[15] there is the conclusion that "dietary fat intake and blood cholesterol levels explain less than is often claimed." This report also sounds "notes of caution about special fat diets for heart and artery disease." It does not seem wrong then that all clinical observations be made known to practicing physicians—even when there is only a hint of some potential adverse reaction—and allow them to decide where the weight of evidence lies. As with all matters in medicine only the treating physician can properly evaluate all relevant factors and decide on the therapeutic approach. Any study that might lead to the prevention of heart disease including Dr Baldwin's own MRFIT Clinical Center at Harvard, cannot help but have the support of physicians just as they support motherhood. But let there also be the right to temper as yet unproved hypotheses with moderation just as Harvard's Department of Nutrition has the right *not* to be for apple pie.

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Congenital absence of circumflex coronary artery

To the Editor

We were interested to read the article by Barresi and associates in the December 1973 issue of THE JOURNAL entitled, Congenital absence of the circumflex coronary artery We are presently preparing for publication an analysis of 20 examples of anomalous origin of the circumflex coronary artery as a branch of the proximal right coronary artery or from the right sinus of Valsalva near the origin of the right coronary artery which we have observed among approximately 3 200 coronary arteriograms performed in our laboratory We would like to make two comments relevant to the Barresi article

1 It is entirely possible to selectively opacify the left and right coronary arteries without the faintest demonstration of an anomalous circumflex artery if it does not arise as a discrete branch of the right coronary artery

2 A consistent finding on left ventriculography done in a right anterior oblique projection in such patients is evidence of the anomalous artery as it passes posteriorly around the right sinus of Valsalva This sign is evident on the aortic root injection labeled Fig 8A, p 815 which we assume to be a lateral and thus closely analogous projection. We include a cine frame from a right anterior oblique left ventriculogram in a patient with a circumflex coronary artery which arises *anomalously from the right sinus of Valsalva*

In our opinion it is unsound to hypothesize in adults that significant areas of left ventricular myocardium can be hypoperfused because of congenital absence of arterial inflow We likewise do not find it difficult to rationalize the normal electrocardiograms normal vector cardiograms and benign clinical course of the two patients described by Barresi and associates in the absence of selective angiographic demonstration of the circumflex coronary artery We would suggest that a repeat coronary arteriogram with emphasis on finding an anomalous circumflex coronary artery arising from a separate ostium just *posterior and/or inferior to the* origin of the right coronary artery might prove of great interest in these two patients

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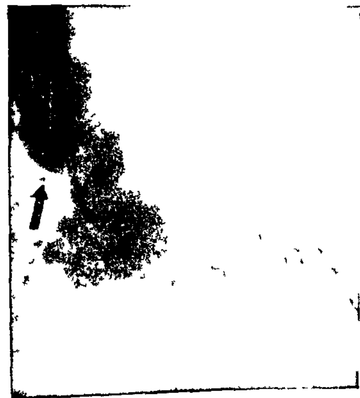


Fig 1 Cine frame from right *anterior* oblique left ventriculogram in a patient with a circumflex coronary artery which arises anomalously from the right sinus of Valsalva The anomalous artery is indicated by the arrow

Reply

To the Editor

The comments of Drs Page and Engel are much appreciated

The variations in the anatomy of the circumflex artery are well known and several important references were cited in the opening lines of our discussion Our real concern about the possibility of anomalous origin of the circumflex artery in patient D M prompted further angiography one week after the original study

The figure in question in our *report* is a right anterior oblique projection (not a lateral) of the aortic root We believe that the area described by Page and Engel represents a superimposition of the partially filled *proximal* portion of the right coronary artery upon the cusp of the aortic valve (Fig 9 of our report shows the vessel to have an unusually large upward proximal bend and an early *origin* of the acute marginal branch) Viewing the aortogram in motion clearly demonstrates this

In our laboratory over 4 500 patients have *undergone* cardiac catheterization in the past five years between 55 and 60 *per cent* have had coronary arteriography This experience

suggests that a normal caliber circumflex vessel originating in close proximity to the ostium of the right coronary artery ought to be readily cannulated. Despite our efforts we were unable to accomplish this. In addition selective cusp injections and aortograms were performed in both patients and an accessory ostium could not be demonstrated in either case. Ventriculograms were performed in both patients and neither one demonstrates the sign described by Page and Engel.

A vessel which courses posteriorly and is visualized during ventriculography ought to be seen equally well during aortography in the RAO projection, if the ostium is patent. In fact, it would seem that aortography would offer a better view of that vessel since the opacified ventricle would tend to obscure it.

We have made no effort to hypothesize that a portion of the myocardium is underperfused. We have, in fact, emphasized the magnitude of the distribution of the right coronary artery in both patients. All available clinical information, to the extent that it has been obtained, suggests that the myocardium is not ischemic.

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Cardiotoxicity of alcohol

To the Editor

The recent article by M. Wong in this JOURNAL (86 508 Oct. 1973) attempts to clarify the conflicting results reported for the effect of alcohol on the heart. Briefly the author explains the contradictory data on a number of factors often found to be responsible for this kind of dilemma—different anesthetic agents and animal species used, open or closed chest measurements, presence or absence of heart disease, dose and method of alcohol administration etc. The main thrust of her argument however is reserved for emphasizing that alcohol does indeed have a dual effect—a direct depressing effect on the myocardium which is offset by the stimulating effect of catecholamines released by alcohol. It is noteworthy that the two articles cited by the author report that high circulating levels of ethanol (up to 900 mg per 100 ml.) failed to significantly affect the hemodynamic performance of the heart (Webb et al. Chest 52 602 1967; Mierzwiak Clin Res. 15 215 1967). In other studies using isolated heart perfusion this lack of response to alcohol was repeatedly demonstrated. However perfusion with even small doses of acetaldehyde 0.1 to 0.2 mM produced profound hemodynamic and metabolic effects (James, T. N. and Bear E. S. AM. HEART J 74 240 1967; Gailis, L. and Verdy M. Can. J Biochem. 49 227 1971). The heart does not contain alcohol dehydrogenase the enzyme required for oxidation of alcohol to acetaldehyde (Chernick G. R. and Leevy C. M. Biochim. Biophys Acta 107 29 1965) and the heart is unable to metabolize alcohol (Lochner A. R. Colley R. and Brink AM HEART J 78 770 1969; Gailis, L., and Verdy M. ibid. James, T. and Bear E. ibid.)

The depressant effect of alcohol, if any must be indirect, e.g. by affecting oxidative metabolism. However aldehyde dehydrogenase has been found in myocardium and the metabolism of acetaldehyde to acetate and CO_2 albeit limited, has been demonstrated (Forsythe G. W. Alexander C. S. and Nagasawa, H. T.: Proc Soc Exp Biol Med. 144 498 1973). Administration of acetaldehyde to man in a dose of 2 to 7 mg per kilogram causes slowing of the heart presumably by activating the baroreceptors (Assmussen E. et al. Acta Pharmacol. 4 311 1948) but most of the cardiotoxic effects of acetaldehyde in man have been seen with the use of alcohol and Antabuse a drug which inhibits the oxidation of acetaldehyde and therefore exposes the heart to relatively high levels of circulating acetaldehyde (Markham J. D. and Hoff E.C. J.A.M.A. 142 1597 1953). Thus to advance Wong's thesis one step further—the cardiotoxicity of alcohol probably resides in its first oxidation product, acetaldehyde which acts indirectly by releasing catecholamine (epinephrine from the adrenal medulla and norepinephrine from the myocardium). It may also interfere with the normal synthetic and degradative pathways of catechol metabolism with the end result of exposing the heart to high concentrations of catecholamines as well as to other intermediate compounds such as catecholaldehydes whose effects on the myocardium are unknown.

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Reply

To the Editor

Dr. Alexander's thesis that the cardiotoxicity of alcohol resides with acetaldehyde either by its release of catechol amines or by its formation of inoperative neurotransmitters, is supported by the literature. However the published accounts are mixed, probably for all of the variables mentioned, and there are preliminary reports[1,2] which describe only the depressive effect on the heart by acetaldehyde that is dose related.

I can accept the acetaldehyde thesis (it fits our data) on a tentative basis, but I cannot deny the evidence for ethanol's direct toxicity on the cell and organism, that is evidence in addition to those acute studies showing immediate hemodynamic depression. If cardiotoxicity can be viewed in the broad sense of affecting the integrity of the myocardial cell and its functions of energy maintenance impulse formation and mechanical contraction there is direct and indirect information collected mostly in the absence of acetaldehyde that alcohol is the one. Gimeno and colleagues[3] demonstrated that ethanol in concentrations of 110 to 880 mg per kilogram per 100 ml. shortens the action potential and depresses contractility of isolated rat atrium. Isreal Jacard and Kalant[4] measured progressive losses of intracellular potassium and of electrical impulse formation with increasing concentrations of ethanol. The observations were made in diverse (noncardiac) tissues from different species and they postulated that alcohol in low concentrations inhibited active transport. The numerous investigations on brain slices and nerve cells which lack significant alcohol dehydrogenase activity indicate that alcohol inhibits action potential, active transport and membrane (Na + K) ATPase.[5]

In intact dogs Regan and associates[6] measured increasing

concentrations of potassium and inorganic phosphate in the coronary sinus effluent as evidence of myocardial necrosis 90 minutes after the start of alcohol infusions at 15 mg per kilograms per minute and 75 minutes after the onset of left ventricular dysfunction Wendt and associates[7] showed loss of myocardial isocitric dehydrogenase in alcoholic noncardiac subjects 30 minutes after the ingestion of 6 ounces of vodka which had minimal effect on the cardiac output Acetaldehyde and catecholamines cannot be completely excluded as causative factors in these two studies Our own data[8] on canine endomyocardium biopsied transvenously from the right ventricle showed that by 15 minutes, alcohol infused at 23 to 30 mg per kilograms per minute caused significant increases in cardiac triglyceride concentration Cardiac performance had also declined significantly in the same period. These rapid changes argue against the acetaldehyde theory because of the latency in its catecholamine release and consequence

I singled out the work by Webb and associates[9] in part to illustrate that the same laboratory using a different preparation can make observations and interpretations at variance with their own earlier experiments carried out in another model Mierzwiak and associates[10] used the same preparation as Webb and associates, made similar observations, and came to a different conclusion

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Return to sinus rhythm after atrial fibrillation

To the Editor

The case report by Zimmerman Basta and January (AM. HEART J 86 676 1973) of three patients who spontaneously developed sinus rhythm after more than ten years of atrial fibrillation is most interesting and suggests that atrial fibrillation of long duration does not always result in changes in the atrial myocardium that make the resumption of sinus rhythm impossible. More data on this problem may be obtained by studies of atrial myocardium obtained during cardiac surgery or autopsy [1]

In 1955 Lewis[2] described three patients who spontaneously returned to sinus rhythm after 11 to 17 years of atrial fibrillation Two of his patients had chronic rheumatic heart disease and one had a cardiomyopathy Neither of the patients with rheumatic heart disease had been operated on. The autopsy data on Patients 1 and 3 described by Lewis were reviewed in our files No histologic studies were made of the atrial myocardium Patient 1 had slight dilatation of both atria The coronary arteries were only slightly diseased The ventricular myocardium revealed only moderate scattered areas of fibrosis Patient 3 had a markedly dilated left atrium without atrial thrombosis

Burch[3] reported a patient who reverted to normal rhythm after 22 months of atrial fibrillation. After eight months of normal rhythm atrial fibrillation returned for eight months, when a normal rhythm again appeared. Fogel[4] in 1943 reported reversion to sinus rhythm after 11 years of atrial fibrillation Vaisrub[5] reported on a patient in whom atrial fibrillation of 37 months duration reverted to normal rhythm Spontaneous reversion of atrial fibrillation to sinus rhythm is not uncommon after mitral valve surgery but this usually occurs within a few weeks after surgery[6] hence the patients described by Zimmerman and associates are unique.

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Reply

To the Editor

We appreciate the comments from Drs Hultgren and Rytand and particularly the historical review Their observations attest to the fact that spontaneous return of sinus rhythm after several years of established atrial fibrillation is probably quite rare. Pathologic studies of hearts from patients with long standing atrial fibrillation consistently show extensive damage to SA node internodal pathways and atrial wall.[1-3] It would therefore be of substantial interest to examine hearts from patients in whom sinus rhythm resumed after chronic atrial fibrillation It is unfortunate that the cases reported earlier by Lewis, whose pathologic reports are referred to by Drs Hultgren and Rytand did not include information about histologic changes in the atria

Reports on similar cases including histopathologic data are awaited with great interest

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Continuous administration of Dilantin

To the Editor

In the article "Drug therapy of heart disease in pediatric patients Part II" by Rutkowski, Cohen and Doyle (this JOURNAL 86 270 1973) the authors mention the use of diphenylhydantoin by "a continuous infusion for treatment of serious digoxin toxicity in infants and children We believe this point needs some clarification

The addition of commercially available sodium diphenylhydantoin solution (Dilantin, Parke Davis) to intravenous infusion is not recommended due to lack of solubility and resultant precipitate[1] Virtually every parenteral incompatibility guide searched recommended that diphenylhydantoin solution be administered without further dilution[2-4] These cautions are a result of the special diluent utilized for intravenous Dilantin. The diluent contains 40 per cent propylene glycol and 10 per cent alcohol in water for injection adjusted with sodium hydroxide to pH 12 However this precaution must be evaluated in view of the situation Due to the emergency nature of this therapy the choice of vehicle and time required for completion of the infusion are critical in obtaining the desired response.

Precipitation of a solution of Dilantin, 250 mg. per liter is reported to occur in less than one hour in many solutions that contain dextrose[5] Frank[6] reported that precipitation can occur even when a stable piggyback solution of Dilantin is administered through an existing intravenous line carrying a dextrose vehicle Chan[7] reported that when Dilantin (100 mg as a ready mixed solution supplied in a 2 ml ampul) is added to 25 to 50 ml of normal saline for injection, microcrystals occur immediately and macrocrystals can be visualized 10 to 15 minutes later

We realize that the continuous or piggyback method is often used in hospitals where nurses cannot give intravenous pushes. However the recommended method of administration of intravenous Dilantin should definitely be by intravenous push

Thus when intravenous Dilantin is to be administered the physician should consider the possibility that continuous or piggyback infusion of Dilantin will give unpredictable results, a situation that one does not desire when treating digitalis toxicity in infants.

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Reply

To the Editor

We appreciate the letter by Drs. Copple and Cluxton concerning the continuous intravenous administration of diphenylhydantoin

After checking with the drug manufacturer we found that in fact diphenylhydantoin can be given in a continuous intravenous drip *but* it does require constant close observation of the solution for flocculation, which does occur especially with dextrose containing solutions Therefore, it is safer and more realistic even in an intensive-care unit setup to administer the drug by intravenous push.

Therefore we amend our recommendation Diphenylhydantoin in the treatment of digitoxicity in the pediatric age group should be given in a dose of 2 to 3 mg per kilogram of body weight as an initial intravenous push. This should be given slowly not to exceed 50 mg. per minute The same dose

may be repeated times twice in 5 to 10 minute intervals Dur ing this time electrocardiogram blood pressure and respira tion should be closely monitored

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Pulmonary emboli associated with transvenous pacemaker

To the Editor

A 71 year old man (O F) with a history of myocardial in farction several years previously was admitted to this hospi tal *the Weirton General Hospital in July 1973 with signs* and symptoms suggesting increasing myocardial damage A transvenous pacemaker was inserted by his attending physician on July 31 1973 He was readmitted on August 18



Fig 1 Photomicrograph lung A 73 24 showing organized structure filling a pulmonary vessel (Hematoxylin and eosin Original magnification × 75)

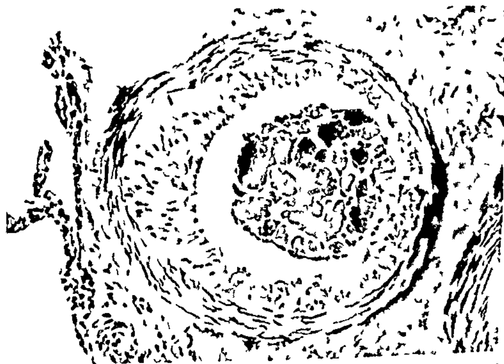


Fig 2 Photomicrograph lung A 73 24 showing more detail of embolus within a pulmonary vessel (Hematox ylin and eosin Original magnification × 340)

1973 and had progressive myocardial disease with signs pointing to another myocardial infarct. He died two and-one-half weeks after entry

Autopsy revealed extensive recent and healing myocardial infarct. In addition a striking finding was noted in the lung The lung sections revealed an organized structure within the lumina of pulmonary vessels, with the following characteristics—this organized structure an embolus almost fills the lumen of one vessel most striking is the presence of deeply acidophilic blocks and intervening loose fibrillar tissue with apparent endothelial cell surface (see Figs 1 and 2)

The over all histopathology suggests to the examiner an origin from heart muscle and very likely the embolus represents a piece of heart muscle dislodged by the tip of the pace maker Another possible explanation for the symmetry and organization of the structure described is a fibrin clot which has become covered with endothelium, and subsequently dislodged.

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Book reviews

Myocardial Diseases Edited by Noble O Fowler MD New York and London 1973 Grune & Stratton, Inc 379 pages Price $18 50

The recent surge of interest in cardiomyopathy makes Fowler s book on myocardial disease timely This book edited by Fowler consists of presentations by 23 contributors They discuss history classification and diagnosis, clinical manifestations and cause morphologic changes, hemodynamic and metabolic features radiologic manifestations changes in the electrocardiogram and vectorcardiogram as well as specific types of cardiomyopathies. The presentations are clear well illustrated and well supported with references to the medical literature The contributions are clinically oriented. The subject is important and the book is a good one which should interest physiologists, pathologists, and clinicians.

Noninvasive Technics in Cardiology By Howard H Wayne MD Chicago 1973 Year Book Medical Publishers, Inc 229 pages

Wayne has produced a paperback monograph of the phonocardiogram apexcardiogram and systolic time intervals techniques used in cardiology He summarizes very well the principles and applications of these methods This book should interest those who are prone to the use of gadgets in cardiology Nevertheless, the most useful noninvasive techniques in cardiology are history taking physical examination and simple laboratory procedures Publications today seem to ignore bedside cardiology including the stethoscope a simple instrument Even though Wayne s book is a good one practicing physicians will find it of little value to them Those interested in the three techniques discussed, on the other hand, will appreciate the monograph The numerous illustrations are well selected and the accompanying text is clear

Medical Managements of Primary Hypertension By Lot B Page MD and James J Sidd MD Boston 1973 Little Brown & Company 103 pages

This small book contains the papers previously published in the *New England Journal of Medicine* on the medical management of primary hypertension The authors review for the practicing physicians the methods of diagnosis and treatment of this common disease They also discuss briefly the drugs commonly used in treatment of hypertension This is a practical discussion about an extremely important disease of adults It is highly recommended as a good book for clinicians

Hypertension Mechanisms and Management Edited by Gaddo Onesti MD Kwan Eun Kim MD and John H Moyer MD New York and London 1973 Grune & Stratton Inc 902 pages Price $39 00

This publication on hypertension of the twenty sixth Hahnemann Symposium is an excellent one The emphasis, of course is on management and mechanisms The contributors discuss definition measurement causes manifestations action of drugs new drugs and therapy complications and the common types of hypertension The contributors are numerous there being 234 from many different nations This book of about 900 pages reviews the problems of hypertension very well Clinicians will find this a very useful book and a good presentation of the existing concepts on hypertension It is intended for the doctor in practice

Coronary Angiography By Harold A Baltake MD Kurt Amplatz, MD and David C Levin, MD Springfield Ill 1973 Charles C Thomas Publisher 239 pages. Price $22 50

This book on coronary angiography is concerned with an important subject The technique is being used more all the time throughout the world. The authors discuss the history methods and interpretations of coronary angiograms. The authors included a discussion of electrocardiographic and hemodynamic changes that occur during the procedure as well as the pitfalls There is also a chapter on postsurgical coronary angiograms. The illustrations and legends are excellent This is a fine book It is well written and presents the procedures in a clear concise and thoughtful manner Physicians in all fields of cardiology will find this to be a valuable book.

Koronarinsuffizienz Periphere Durchblutunsstorungen By U Gottstein Stuttgart Wien 1973 Verlag Hans Huber Bern 321 pages

This small paperback book by many contributors summarizes the present concepts in Germany concerning coronary artery disease and myocardial ischemia The etiology and pathogenesis of coronary atherosclerosis as well as methods for quantitating the degree of atherosclerosis are discussed The role of coronary angiography cardioangiography ventriculography and other techniques currently employed in the cardiac catheterization laboratory are also included among the presentations. There is a brief review of the peripheral arterial circulation but the book is primarily concerned with coronary heart disease rather than peripheral arterial disease Both have much in common This is a good book concerned primarily with the common problems related to angiology

Kreislaufstillstand und Wiederbelebung (Cardiac Arrest and Resuscitation) ed 3 By Martin Stauch MD Stuttgart, 1973 Georg Thieme Verlag 92 pages.

In spite of the small size (5 by 7½ inches, 92 pages) this book is quite comprehensive including the important aspects of diagnosis types causes and treatment of cardiac arrest with 104 references and a subject index of three pages. It starts with a quotation from Safar (J A M A 167 335 1958) Cardiac arrest is the clinical picture of cessation of circulation in a patient who was not expected to die at the time The main parts of the book are diagnosis of cardiac arrest resuscitation of pulmonary ventilation (manual and with respirators) artifical circulation (mainly massage manual and instrumental with discussion of efficiency and complications) types of cardiac arrest. asystole and ventricular fibrillation. A rare type of cardiac arrest—absent cardiac contraction in presence of QRS complexes—is listed (p 33) of the 24 patients reported none survived Treatment of cardiac arrest (drugs, electrical pacemaker defibrillation) pp 34 to 49 is practically the most important part of the book followed by

'Treatment after successful resuscitation (pp 50 to 54) Causes of cardiac arrest (cardiac diseases conduction defects PVC s reflex cardiac arrest digitalis and quinidine intoxication electrolyte disturbance etc) are *discussed on pp 56 to 73 followed by Prevention of car*diac arrest" (including ECG monitoring) It is not surprising that within the relatively short time of five years a third edition has appeared. It can be recommended without reservation

Books received

How To Live With A Heart Attack. By Robert A Miller M.D Radnor Pa. 1973 Chilton Book Company 236 pages Price $6 95

Medical Aspects of Exercise Testing and Training Edited by Lenore R Zohman, M D and Raymond E Phillips M D New York, 1973 Intercontinental Medical Book Corp 188 pages Price $12 50

Pharmacological Modifications of Evoked Brain Potentials By A A Borbely Stuttgart, 1973 Hans Huber Publishers 138 pages

Coronary Care. By Norman L Goodland, S R N., R N.M.S Baltimore 1973 The Williams & Wilkins Co 88 pages. Price $7 75

Catheter Center. By Martin Hanig Ph.D., Pacific Grove Calif 1973 Boxwood Press, 141 pages. Price $2 95

Neonatology Diseases of the Fetus and Infant Edited by Richard E Behrman, M.D., St. Louis, 1973 The C V Mosby Company 698 pages Price $39 50

Announcements

Prostaglandins in clinical medicine

The University of Texas Health Science Center at Houston Medical School Division of Continuing Education and Baylor College of Medicine will present a workshop on the prostaglandins in clinical medicine on Sept 19 1974 at Houston Texas This workshop will review and update the clinical applications and implications of the prostaglandins. Their role in pregnancy abortion the gastrointestinal tract heart kidney platelet metabolism and other uses will be presented by investigators and clinicians in the forefront of this exciting development

For further information write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Sixth International Congress of Nephrology

The Sixth International Congress of Nephrology will be held from June 8 through June 12 1974 at the Palazzo dei Congressi in Florence Italy For further information please write to the Secretariat Scientific Program Committee Nephrology Dialysis Department S Orsola University Hospital, Via Massarenti 9 40138 Bologna Italy Telephone (051) 390923 Social Program Committee Institute of Urology University of Florence Viale Pieraccini 18 50139 Firenze Italy Telephone (055) 417645 Travel agent Wagons LitsCook Piazza Strozzi 15/R 50100 Firenze Italy Telephone (055) 28142/43/44

Eighth Annual Workshop in Electrocardiography

The Rogers Heart Foundation announces the eighth annual Workshop in Electrocardiography under its sponsorship *for physicians and nurses* to be held at the Sheraton Olympic Villas, Orlando Fla from June 17 through June 22 1974 The director is Henry J L Marriott, M D For further details please write Rogers Heart Foundation Inc St Anthony's Hospital St. Petersburg Fla. 33705 Telephone (813) 894 0790

Erratum

In the article Electrocardiographic changes during hyperventilation resembling myocardial ischemia in patients with normal coronary arteriograms (Am. Heart J 87 383 390 1974) by Lary and Goldschlager panel D of Figure 6 was inadvertently flopped so that it appears upside down. The D should of course appear *in the lower* left hand corner of the illustration the strokes should be at the top and the heavy wavy line should be at the bottom

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